ความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต

นาง ปรียา จาโกต้า

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2552

THE PREVALENCE OF RESTLESS LEGS SYNDROME IN THAI PATIENTS WITH PARKINSON'S DISEASE AND PATIENTS TAKING NEUROLEPTIC DRUGS

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Thesis Title	THE PREVALENCE OF RESTLESS LEGS SYNDROME IN THAI PATIENTS WITH PARKINSON'S DISEASE AND PATIENTS TAKING NEUROLEPTIC DRUGS
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ปรียา จาโกต้า : ความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต (THE PREVALENCE OF RESTLESS LEGS SYNDROME IN THAI PATIENTS WITH PARKINSON'S DISEASE AND PATIENTS TAKING NEUROLEPTIC DRUGS) อ. ที่ปรึกษาวิทยานิพนธ์หลัก : รศ. นพ. รุ่งโรจน์ พิทยศิริ, อ. ที่ปรึกษาวิทยานิพนธ์ร่วม : ผศ. นพ. ธนินทร์ อัศวเชียรจินดา ; 60 หน้า

ที่มาของปัญหา: กลุ่มอาการขาอยู่ไม่สุขเป็นโรคที่พบบ่อย แต่มักถูกวินิจฉัยน้อยกว่าความเป็นจริงทั้งๆที่เป็นโรคที่สามารถรักษาได้ กลุ่มอาการขาอยู่ไม่สุขตอบสนองดี ต่อยากลุ่มที่เสริมฤทธิ์สารโดปามีน (dopaminergic drugs) แม้กระทั่งให้ยาในปริมาณน้อย มีการศึกษาถึงความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยโรคพาร์กินสันในบางประเทศ แต่ไม่มีการศึกษาถึงความชุกในผู้ป่วยที่รับประทานยารักษาโรคจิต ซึ่งทั้งสองเป็นภาวะของการขาดสารโดปามีนในระบบประสาทส่วนกลาง

วัตถุประสงค์: เพื่อศึกษาหาความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน และผู้ป่วยที่รับประทานยารักษาโรคจิต

วิธีวิจัย: การสัมภาษณ์อาการของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยโรคพาร์กินสันที่มาตรวจที่คลีนิคกลุ่มโรคความเคลื่อนไหวผิดปกติ และผู้ป่วยที่รับประทานยารักษาโรคจิตที่มาตรวจที่คลีนิคจิตเวชของโรงพยาบาลจุฬาลงกรณ์ ซึ่งผ่านเกณฑ์การคัดเลือก ผู้ป่วยที่มีประวัติโรคไตวายเรื้อรัง ปลายประสาทเสื่อม โรคไขสันหลัง และมะเร็ง จะถูกคัดออก ผู้ป่วยได้รับการตรวจเลือดดูระดับเฟริติน

ผลการวิจัย: ผู้ป่วยโรคพาร์กินสันที่เข้าร่วมการวิจัยมีทั้งหมด 183 ราย มีผู้ป่วยเพียง 3 รายเท่านั้นที่ตรงตามหลักเกณฑ์ การวินิจฉัยกลุ่มอาการขาอยู่ไม่สุข (1.6%) หนึ่งในผู้ป่วย 3 ราย มีระดับเฟริตินในเลือดเท่ากับ 31.9 ng/ml เมื่อคัดผู้ป่วยรายนี้ออก ความชุกของกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยโรคพาร์กินสันจะลดเหลือ 0.98%

ผู้ป่วยที่รับประทานยารักษาโรคจิตที่เข้าร่วมการวิจัยทั้งหมด 100 ราย มีผู้ป่วยเพียง 1 รายเท่านั้นที่เป็นกลุ่มอาการขาอยู่ไม่สุข (1%) ผู้ป่วยรายนี้เป็นผู้ป่วยหญิงอายุ 40 ปี ซึ่งได้รับการวินิจฉัยว่าเป็นโรคซึมเศร้า ผู้ป่วยเริ่มมีอาการกลุ่มอาการขาอยู่ไม่สุขหลังรับประทานยา perphenazine 4 ปี เมื่อหยุดยา perphenazine อาการของกลุ่มอาการขาอยู่ไม่สุข มีความถี่และความรุนแรงน้อยลง แต่ไม่หายไป

สรุป: ความชุกของกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิตนั้นต่ำ ดังนั้นนอกจากการทำงานที่ผิดปกติของระบบโดปามีนในสมองแล้ว น่าจะมีปัจจัยอื่นๆ ในการทำให้เกิดกลุ่มอาการขาอยู่ไม่สุขร่วมด้วย

ภาควิชา .....อายุรศาสตร์..... ลายมือชื่อนิสิต .....

สาขาวิชา .....อายุรศาสตร์..... ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา .....2552..... ลายมือชื่ออ.ที่ปรึกษาวิทยานิพนธ์ร่วม.....

5174869830: MASTER OF MEDICAL SCIENCE PROGRAM

KEYWORD: RESTLESS LEGS SYNDROME/ PARKINSON'S DISEASE/ NEUROLEPTICS/ FERRITIN

PRIYA JAGOTA: THE PREVALENCE OF RESTLESS LEGS SYNDROME IN THAI PATIENTS WITH PARKINSON'S DISEASE AND PATIENTS TAKING NEUROLEPTIC DRUGS. THESIS ADVISOR: ASSOC. PROF. ROONGROJ BHIDAYASIRI. THESIS CO-ADVISOR: ASSIST. PROF. THANIN ASAWAVICHIENJINDA, 60 pp.

Background: Restless legs syndrome (RLS) is a common neurologic disorder which is underdiagnosed in all parts of the world in spite of being treatable. The symptoms of RLS are very responsive to dopaminergic medications even at a very low dose. There have been several studies looking at the prevalence of RLS in Parkinson's disease (PD) patients in other countries and no study in patients taking neuroleptic drugs from any cause – both being conditions of CNS dopamine deficiency.

Objectives: To study the prevalence of RLS in Thai PD patients and Thai patients taking neuroleptic drugs.

Methods: PD patients were consecutively interviewed from movement disorders clinic for RLS symptoms and patients taking neuroleptic drugs were consecutively interviewed from psychiatry clinic of Chulalongkorn Hospital. Diagnosis of RLS was made according to the NIH-IRLSSG diagnostic criteria. Serum ferritin level was checked in patients with and without RLS. Patients with end-stage renal disease, peripheral neuropathy, spinal cord diseases and malignancy were excluded from the study.

Results: For PD patients, three out of 183 patients interviewed (1.6%) had symptoms consistent with RLS. When one patient who had a serum ferritin level of 31.9 ng/ml is excluded, the prevalence falls to 0.98%.

For patients taking neuroleptic drugs, only one out of 100 patients had symptoms consistent with RLS (1%). She was a 40 year old female with a diagnosis of depression. She started having RLS symptoms approximately four years after starting perphenazine. The symptoms persisted after the medications were discontinued though they decreased in frequency and severity.

Conclusions: The prevalence of RLS in Thai PD patients was found to be much lower than in most of the previous studies, especially those conducted in Europe and America. The prevalence of RLS in patients taking neuroleptics is also low. Other factors apart from dopaminergic dysfunction are likely to be involved in the pathogenesis of RLS.

Department: .....Medicine..... Student's Signature: .....

Field of Study: .....Medicine..... Advisor's Signature: .....

Academic Year: .....2009..... Co-Advisor's Signature: .....

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LIST OF ABBREVIATIONS

CNS:	Central nervous system
CI:	Confidence interval
CSF:	Cerebrospinal fluid
DA:	Dopamine agonist
DBS:	Deep brain stimulation
ESRD:	End stage renal disease
H&Y:	Modified Hoehn and Yahr staging
123I-IBZM:	[123I]-(S)-2-hydroxy-3-iodo-6-methoxy-[(1-ethyl-2-pyrrolidinyl)methyl] benzamide
IRLSSG:	International Restless Legs Syndrome Study Group
LDED:	Levodopa equivalent dose
MRI:	Magnetic resonance imaging
NCV:	Nerve conduction study
NIH:	National Institute of Health
PD:	Parkinson's disease
PET:	Positron emission tomography
RLS:	Restless legs syndrome
RLS-SFDQ13:	Cambridge-Hopkins Restless Legs Syndrome Short Form 2 Diagnostic Questionnaire
SPECT:	Single photon emission computed tomography
TIBC:	Total iron binding capacity

CHAPTER I

INTRODUCTION

1.1 Background and Rationale

Restless legs syndrome (RLS) is a common neurologic disorder which is underdiagnosed[1] in all parts of the world in spite of being treatable. RLS can be diagnosed when a patient has all the four symptoms listed in the International Restless Legs Syndrome Study Group (IRLSSG) essential diagnostic criteria[2] (see operational definition (chapter 3) for the criteria). The prevalence of RLS in the REST general population study, conducted in the USA and five other European countries, was 7.2%. Among them 2.7% suffered from the symptoms and had significant impairment in sleep and quality of life[3]. Those who had symptoms at least twice a week had a quality of life similar to other chronic diseases such as type 2 diabetes mellitus and depression[3]. Iron deficiency, uremia and pregnancy are among the confirmed risk factors for RLS. In addition, RLS has been found to associate with certain conditions such as Parkinson's disease (PD), neuropathy and spinal cord diseases such as MS. There have been case reports of neuroleptic-induced RLS and RLS in patients with hemochromatosis.

CNS dopaminergic abnormality and CNS iron insufficiency are the two main causes of RLS[4]. It has been postulated that all conditions that compromise iron status increase the risk of RLS and that the changed or reduced CNS iron status produces RLS symptoms largely through its effects on the dopaminergic system[4]. The symptoms of RLS are very responsive to dopaminergic medications even at a

ต้นฉบับไม่มีหน้า 2

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very low dose and a response to dopaminergic agents strongly supports the diagnosis of RLS.[2] Current guidelines suggest dopamine agonists as the first-line treatment of daily RLS.[5] Autopsy studies show no dopaminergic cell loss[6]. This may indicate that there is no neurodegenerative process of the dopaminergic system in RLS but rather a dopaminergic dysfunction. Genetic factors are especially important in idiopathic and early-onset RLS[6].

As the symptoms of RLS are very responsive to dopaminergic medications it can be hypothesized that dopamine blocking agents such as neuroleptics can cause RLS.

There have been several studies on the prevalence of RLS in PD in several countries including Japan, India, Singapore, USA and Spain. The prevalence varied greatly in these studies ranging from 0%[7] to 20.8%[8]. To our knowledge there has been no study looking at the prevalence of RLS in patients taking neuroleptics for any cause of psychiatric illness. Importantly, no published study on RLS has ever been conducted in Thailand.

1.2 Research Questions

- **Primary research questions:**

  What is the *prevalence* of restless legs syndrome (RLS) in Thai patients with Parkinson's disease?

- **Secondary research questions:**

a. What is the *prevalence* of RLS in Thai patients taking neuroleptic drugs?

b. What is the *severity* of RLS in Thai patients with Parkinson's disease and patients on neuroleptic drugs?

c. What is the prevalence of patients with *family history* of RLS in Thai patients with RLS and Parkinson's disease or patients on neuroleptic drugs?

d. Are there differences in *serum ferritin* level of patients with and without RLS in each group?

1.3 Objectives

a. To study the *prevalence* of RLS in Thai patients with *Parkinson's disease*.

b. To study the *prevalence* of RLS in Thai patients *taking neuroleptic drugs*.

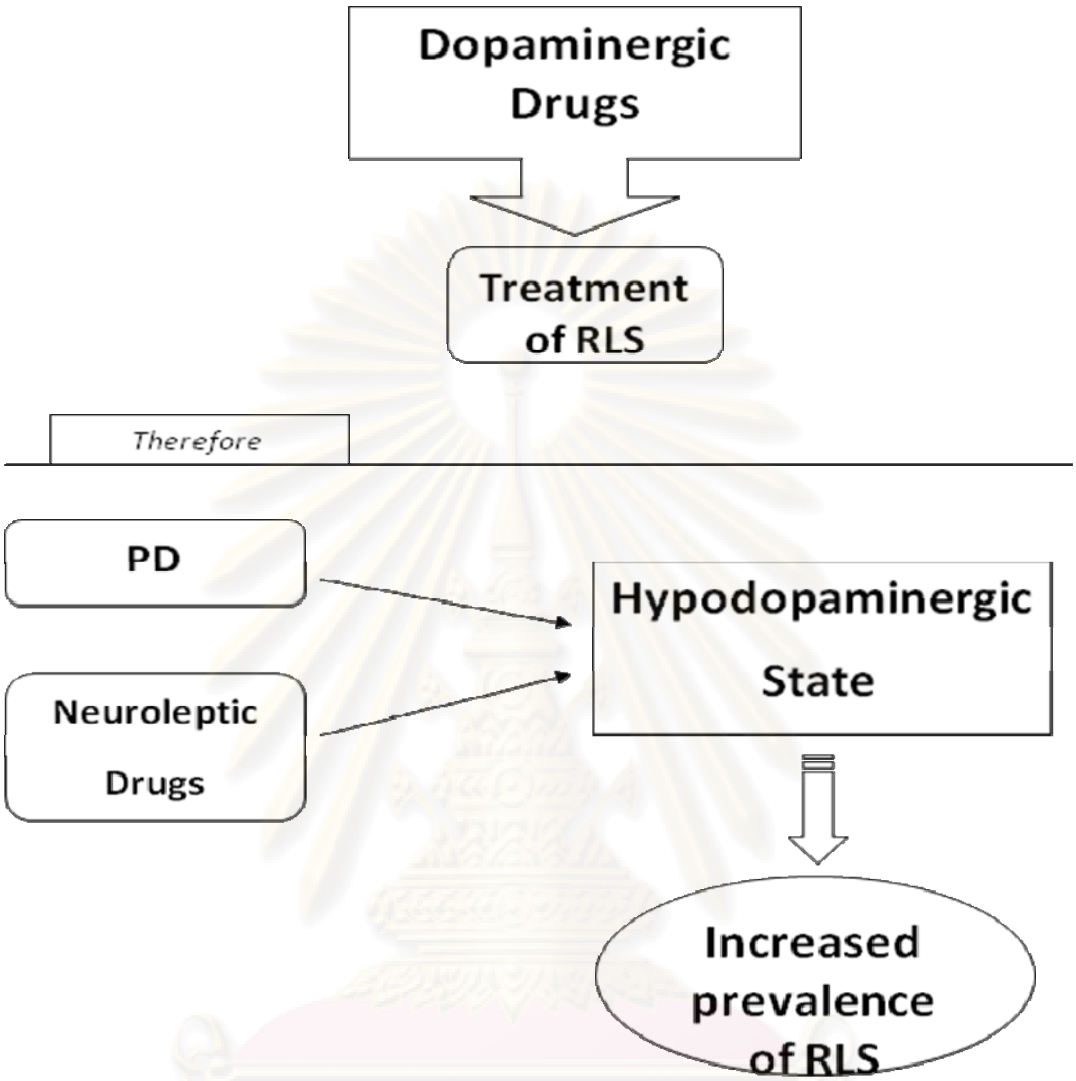
c. To study the *severity* of RLS in Thai patients with Parkinson's disease and patients on neuroleptic drugs.

d. To study the prevalence of patients with *family history* of RLS in Thai patients with RLS and Parkinson's disease or patients on neuroleptic drugs.

e. To study the differences in *serum ferritin level* of patients with and without RLS in each group of patients.

f. To compare the prevalence, severity, family history and serum ferritin level of patients with and without RLS in a disease of dopaminegic cells degeneration (Parkinson's disease) and a state of iatrogenic low CNS dopamine level (patients taking neuroleptic drugs).

1.4 Conceptual Framework



1.5 Assumptions

i. All patients are assumed to take their medicines regularly as prescribed by their physicians

ii. All patients taking neuroleptic drugs are assumed to have good absorption of the medicines making them all in a state of dopamine deficiency while on the medications.

iii. Patients know whether their relatives have symptoms of RLS or not.

1.6 Study Population

Our case population was Thai patients with Parkinson's disease (PD) or non-PD patients taking neuroleptic drugs. Sample of this population was obtained from patients who attended the Chulalongkorn Comprehensive Movement Disorder Clinic at King Chulalongkorn Memorial Hospital for PD patients and patients who attended the psychiatry clinic at King Chulalongkorn Memorial Hospital for non-PD patients taking neuroleptic drugs. Patients were required to be adults above 18 years old. Patients were excluded if they had conditions that could be a cause of secondary RLS. They are patients with history of end-stage renal disease, neuropathy, spinal cord disease, malignancy and patients who were pregnant. Patients with a history of malignancy were excluded since many chemotherapy drugs are known to cause neuropathy.

1.7 Abbreviations

CNS: Central nervous system

CI: Confidence interval

CSF: Cerebrospinal fluid

DA: Dopamine agonists

DBS: Deep brain stimulation

ESRD: End stage renal disease

H&Y: Modified Hoehn and Yahr staging

123I-IBZM: [123I]-(S)-2-hydroxy-3-iodo-6-methoxy-[(1-ethyl-2-pyrrolidinyl)methyl] benzamide

IRLSSG: International Restless Legs Syndrome Study Group

LDED: Levodopa equivalent dose

MRI: Magnetic resonance imaging

NCV: Nerve conduction study

NIH: National Institute of Health

PD: Parkinson's disease

PET: Positron emission tomography

RLS: Restless legs syndrome

RLS-SFDQ13: Cambridge-Hopkins Restless Legs Syndrome Short Form 2 Diagnostic Questionnaire

SPECT: Single photon emission computed tomography

TIBC: Total iron binding capacity

1.8 Expected Benefits and Applications

We hope that the result of our study will increase the awareness of RLS since it is commonly mis- or underdiagnosed while proper treatment can dramatically reduce the symptoms. It will also provide information on various factors which may or may not correlate with the presence of RLS in both conditions. We also hope that it will lead to a better understanding of the symptoms of RLS in these two conditions and help differentiate RLS from other symptoms which are similar to RLS and are commonly present in both the conditions. Examples include motor fluctuations in PD and akathisia in patients taking neuroleptics. These will lead to correct diagnosis of various symptoms, reducing risk factors and proper management.

CHAPTER II

LITERATURE REVIEW

2.1 Restless legs syndrome in Parkinson's disease

Literatures about RLS in PD were searched electronically in medline and Thai Index Medicus databases at the initiation of the project with keywords being 'restless legs syndrome and Parkinson's Disease'. In addition, the reference list of the relevant articles was also searched. Of the 161 items in medline, there were only fourteen items related to RLS and PD by title, and of these only four were original articles looking at the prevalence of RLS in PD patients[7, 9-11]. A search in the reference list of related articles revealed two more literatures looking at the presence of RLS in PD patients[8, 12]. All used the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria for the diagnosis of RLS.

The largest study was done by Ondo et al.[8]. This was a cross-sectional study done by distributing questionnaires at the movement disorders clinic. Patients were interviewed at a later time, both of whom were positive and negative for RLS from the questionnaire. The questionnaire was not validated but this does not interfere with the result since all patients were eventually interviewed. The study did not include any control, did not exclude patients who had conditions that may cause RLS (secondary RLS) and serum ferritin was not obtained in all patients. From 303 PD patients 63 had RLS (20.8%). The incidence is higher than the incidence in general population (7.2%)[3]. Different variables were compared such as age at onset, duration and severity of PD, medications and sleep scales. Serum ferritin level was measured in

some patients. Neither variable could predict the development of RLS symptoms. However, serum ferritin levels were significantly lower in PD with RLS patients compared with PD without RLS patients ($p=0.01$) suggesting that RLS in these patients is likely to be due to iron deficiency. When compared with patients with idiopathic RLS, patients with PD and RLS were older at RLS onset, less likely to have a family history of RLS and had lower serum ferritin levels.

Another cross-sectional study done in Caucasian PD patients was done in Spain by Gomez-Estaban et al.[11]. The literature did not indicate the recruitment method but all the patients who met the inclusion criteria were interviewed, diagnosed according to the IRLSSG criteria and quality of life was also measured. There was no control, secondary RLS were not ruled out and serum ferritin level was not measured. There were 25 patients with RLS out of 114 PD patients (21.9%). This is very similar to the study by Ondo et al. There were also eight patients who underwent STN DBS none of whom developed RLS. Similar to the findings of Ondo et al. none of the clinical characteristics correlated with RLS. However, patients with RLS and PD had poorer sleep scores than patients with PD alone, though the incidence of diurnal hypersomnia was not increased and quality of life was not affected. Serum ferritin level was not obtained and other causes of secondary RLS were not investigated, so it cannot be concluded that the increased incidence of RLS in these patients are directly associated with PD.

There are four studies looking at the prevalence of RLS in Asian PD patients. One is done in Japan by Nomura et al.[10]. It was a controlled, cross-sectional study done in neurology outpatient clinic. There was no significant difference in gender

distribution or mean age between the patients and controls. Moreover, both patients and controls did not have conditions that are known to cause secondary RLS and serum ferritin level was obtained in both patients and control. These points make the study relatively stronger than the other studies. There were 165 PD patients and 131 age- and sex-matched controls most of whom were caretaker of patients at the neurology clinic. There were 20 patients in PD group who fulfilled IRLSSG diagnostic criteria (12%) while there were only three patients in the control group (2.3%). Patients with PD and RLS were younger, had earlier age at onset of PD and poorer quality of sleep compared with patients with PD without RLS. Moreover, the number of young-onset PD patients was significantly higher in the PD with RLS group. In contrast to Ondo et al.'s finding, serum ferritin and iron levels were not different in the two groups. This study suggests a more causal link between PD and RLS since no patients reported conditions known to cause secondary RLS and serum ferritin levels were not different in PD patients with and without RLS.

Another case-controlled cross-sectional study is done in India by Krishnan et al.[9]. Patients were recruited from Movement Disorders clinic. Controls were matched in gender, age, regional background, educational status and social background. All the cases and controls were interviewed and examined personally by one of the authors. The study revealed a 7.9% incidence of RLS in PD patients while the incidence of RLS in the control group was only 0.8%. Patients with PD who had RLS were older and had a higher prevalence of depression compared with those who did not have RLS. Serum ferritin level was obtained in 9 of the 10 patients who had PD with RLS but not in patients without RLS. Five of them had serum ferritin level <50 ng/ml. One of the major drawbacks of this study is that 90% of the PD patients

were male while RLS is predominant in female. Blood glucose, urea and hemoglobin levels were obtained in all patients with RLS and nerve conduction study was done in nine patients with RLS. One patient had a sensory neuropathy. These tests helped ruled out some of the causes of secondary RLS objectively.

None of the 125 PD patients satisfied the IRLSSG diagnostic criteria in a study in Singapore conducted by Tan et al.[7], which was published in 2002. It was a cross-sectional study. Patients from Movement Disorders clinic were consecutively interviewed by a movement disorder specialist. It was a tertiary center so most of the patients were advanced PD cases hence it did not represent true PD population. Validity of the diagnosis was tested on separate occasions, so it is unlikely that patients with RLS were missed. There was no control but similar studies were done in general population (prevalence of RLS was 0.6%) and clinic population (prevalence of RLS was 1%) not long before this study, so the prevalence could be compared. Secondary causes were not ruled out and serum ferritin level was not obtained, but these did not have any effect since no patients in the PD group had RLS.

In another study done in Singapore by Loo and Tan which was published in 2008[12], the result was different from the study mentioned above. The study looked at the consequence of RLS on sleep quality as well. The study was conducted in 200 PD patients and 200 controls. The prevalence of RLS in PD patients was 3% while it was 0.5% in controls. This result was not significant, *p*-value=0.07. None of the patients with RLS had a low serum ferritin level.

Recently, after the conception and initiation of the study, there had been more reports on the prevalence of RLS in PD patients. In Korea, 447 PD patients were interviewed for RLS symptoms, 73 of whom were positive for RLS (16.3%)[13]. This was higher that the result of the prevalence of RLS in Korean general population, which was 7.5%[14]. As with some of the previous studies, secondary causes of RLS were not explored. Interestingly, multivariate logistic regression analysis showed that treatment duration was a significant factor in the development of RLS.

A study conducted in Italy by Calzetti et al.[15] in 118 PD patients and 110 controls found that the prevalence of *primary* RLS in their PD patients was 3.3% and 2.7% in controls. The difference was not statistically significant, *p*-value=0.91. In addition to laboratory tests to rule-out abnormalities that might be a cause for secondary RLS, nerve conduction study (NCV) was also done in patients participating in this study to rule-out neuropathy. Hence, the prevalence is highly probable to be of true primary RLS.

The most recent article published is the study done in Austria by Peralta et al.[16]. One hundred and thirteen PD patients were interviewed by movement disorders specialist. Of these, 28 patients (24%) were diagnosed as RLS. There was no control and causes of secondary RLS were not explored. Patients with RLS were significantly younger, had an earlier onset of PD and received lower levodopa equivalent doses when compared with PD patients without RLS.

Of note, is that there had been reports of the emergence of RLS in PD patients after deep brain stimulation (DBS)[17] and also of improvement of RLS after DBS[18].

The studies show discrepancy of findings. We aim at studying the prevalence of RLS in Thai PD patients and factors that might be associated with the occurrence of RLS in PD.

2.2 Restless legs syndrome in patients taking neuroleptic drugs

Literatures about RLS in patients taking neuroleptic drugs were searched electronically in medline and Thai Index Medicus databases at the initiation of the project with keywords being ‘restless legs syndrome and neuroleptics or antipsychotics’. In addition, the reference list of the relevant articles was also searched. Of the 61 items in medline, there were seven case reports of RLS caused by various neuroleptic drugs[19-25]. A search in the reference list of related articles revealed one literature looking at the presence of RLS in schizophrenic patients[26]. All used the International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria for the diagnosis of RLS.

Case reports regarded on the occurrence of RLS in patients starting certain neuroleptic drugs or the emergence of RLS after escalating the dose. The symptoms resolved after stopping or reducing the offending neuroleptic. These included clozapine[22], haloperidol[25], olanzapine[20, 21], risperidone[19] and quetiapine.[23, 24].

A study by Kang et al.[26] looked at the prevalence, characteristics and clinical correlates of RLS in schizophrenic patients admitted into their hospitals. There were 182 patients and 108 controls. The prevalence of RLS was 21.4% in patients and 9.3% in controls (p=0.009). The study found that RLS was associated with more severe psychiatric symptoms. As the study was conducted in in-patients only and it was found that RLS was associated with more severe disease, it may not represent the true prevalence since most in-patients have more severe disease than out-patients. Moreover, patients with other psychiatric diseases taking neuroleptic drugs were not included in the study.

Recently another case was reported in which RLS was likely to be caused by olanzapine[27].

We aim to look at the prevalence of RLS in patients taking neuroleptics for any cause who did not have any other conditions that could cause secondary RLS.

CHAPTER III

RESEARCH METHODS

3.1 Research Methodology

Study population:

a. Target: Thai patients with Parkinson's disease and non-PD patients taking neuroleptic drugs.

b. Population sample: Patients with one of the above conditions who are getting their treatment at King Chulalongkorn Memorial Hospital from 1st March, 2009 to 28th February, 2010.

c. Inclusion criteria:

- Patients with Parkinson's disease diagnosed according to the UKPDSBB criteria.
- Non-PD patients who are on neuroleptic drugs.
- Adults ≥ 18 years old
- Informed consent

d. Exclusion criteria:

- Intercurrent illness e.g. infections, malignancies
- Patients with the following conditions:
  - End-stage renal disease (ESRD)
  - neuropathy
  - history of spinal cord diseases
  - pregnancy

- Patients will be interviewed for the above conditions and clinical examination will be done in suspected cases.

- Patients in a condition that is not able to give reliable information as judged by the interviewer

e. Study method and sampling technique:

Patients will be recruited as follows:

- Patients with Parkinson's disease will be consecutively sampled from movement disorders clinic at King Chulalongkorn Memorial Hospital.
- Patients taking neuroleptic drugs will be consecutively sampled from psychiatry clinic at King Chulalongkorn Memorial Hospital.

Patients will be interviewed by a neurologist, a movement disorders specialist or a trained interviewer. The interviewer will use the Thai version of Cambridge-Hopkins Restless Legs Syndrome Short Form 2 Diagnostic Questionnaire (RLS-SFDQ13) (appendix D) as a guide for a structured interview. Examples of abnormal sensations (appendix E) will be provided to the patients but they will first be asked to describe the abnormal sensations in their own words. Diagnosis of RLS will be made if the patients fulfill the NIH-IRLSSG diagnostic criteria. Those who are interviewed by a trained interviewer and are positive for RLS will be examined again by one of the investigators.

All patients will be tested for serum ferritin level.

3.2 Sample Size Calculations

The sample size is calculated using the prevalence of RLS in patients with PD from the study done in Japan by Nomura et al.[10] since the study is done in Asians, used the IRLSSG diagnostic criteria, is hospital-based, has a control population and excluded patients with conditions that may cause secondary RLS. The prevalence of RLS in PD patients in this study was 12%.

$$n = (Z_{\alpha/2})^2 \, pq / d^2$$

$$p = 0.12, q = 0.88$$

$$n = (1.96)^2 (pq) / (0.05)^2$$

$$= (1.96)^2 (0.12 \times 0.88) / (0.05)^2$$

$$= 162.27$$

Sample size = 163 patients

Hence, our calculated sample size for PD patients is 163 patients.

3.3 Operation Definitions

Restless legs syndrome:

A patient who fulfils all the four Essential diagnostic criteria for RLS of the National Institute of Health (NIH)-International Restless Legs Syndrome Study Group (IRLSSG) as follows[2]:

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs (Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs)

2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting

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

4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (When symptoms are very severe, the worsening at night may not be noticeable but must have been previously present)

Parkinson's disease:

Patients who fulfill UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria[28] as follows:

Step 1 Diagnosis of Parkinsonian syndrome

* Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)

* And at least one of the following:

- muscular rigidity
- 4-6 Hz rest tremor
- postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

* History of repeated strokes with stepwise progression of parkinsonian features
* History of repeated head injury
* History of definite encephalitis
* Oculogyric crises
* Neuroleptic treatment at onset of symptoms
* More than one affected relative
* Sustained remission
* Strictly unilateral features after 3 years
* Supranuclear gaze palsy
* Cerebellar signs
* Early severe autonomic involvement
* Early severe dementia with disturbances of memory, language, and praxis
* Babinski sign
* Presence of cerebral tumour or communicating hydrocephalus on CT scan
* Negative response to large doses of levodopa (if malabsorption excluded)
* MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease

(Three or more required for diagnosis of definite Parkinson's disease)

* Unilateral onset
* Rest tremor present
* Progressive disorder
* Persistent asymmetry affecting side of onset most
* Excellent response (70-100%) to levodopa

* Severe levodopa-induced chorea

* Levodopa response for 5 years or more

* Clinical course of 10 years or more

Neuroleptics:

Typical neuroleptics/antipsychotics :

- Chlorpromazine
- Fluphenazine
- Haloperidol
- Thioridazine
- Trifluoperazine
- Loxapine
- Perphenazine
- Prochlorperazine

Atypical neuroleptics/antipsychotics :

- Clozapine
- Risperidone
- Olanzapine
- Quetiapine
- Ziprasidone
- Aripiprazole

Severity of RLS:

As no definition for the severity of RLS is available we intend to use the definition of medically significant RLS (frequency at least twice a week, distress at

least moderate) defined “RLS sufferers”, a group most likely to warrant medical treatment[3], in our study.

Family History:

Includes first and second degree relatives.

End-Stage Renal Disease:

Patients with a history of oliguria or anuria, bipedal pitting edema and dry skin will be suspected of having end-stage renal disease.

Neuropathy:

Patients complaining of numbness of hands and/or feet and physical examination revealing hypoesthesia or hyperesthesia will be suspected of having a neuropathy.

3.4 Observation and Measurements

- Demographic and clinical data: Age, gender, drinking and smoking history, clinical diagnosis, duration and onset of each disease, modified Hoehn and Yahr staging (H&Y) for PD patients, family history of RLS, current medications, duration of medications.
- Cambridge-Hopkins Restless Legs Syndrome Short Form 2 Diagnostic Questionnaire (RLS-SFDQ13)[29]: is a validated self-completed questionnaire (appendix F). The questionnaire has been translated into Thai and back translated into english by professional translators. The translated questionnaire was validated

in two RLS patients and in 28 individuals without RLS. There was no false positive or false negative.

- Additional clinical information required for patients with RLS: duration, onset and frequency of the symptoms, and the amount of distress caused by the symptoms.
- Blood test result (serum ferritin level will be measured using "Elecsys 2010" machine). The measured level will be a continuous data.

3.5 Statistical Analysis

Categorical data will be analyzed using frequency and percentage. Continuous data will be analyzed using mean and standard deviation (SD). For non-normal distribution, analysis will be made using median, minimum and maximum values. Estimation of proportion of prevalence will be tested by single proportion Z-test. Correlation between occurrence of RLS and different variables, such as duration of underlying disease (PD or duration of taking neuroleptics) will be sought.

3.6 Ethical Considerations

(See Appendix-B for Information Sheet for Volunteers and Consent Form)

All patients and volunteers will be provided information on this research study and informed consent will be sought for every subject. Whole blood of 4 ml would be drawn from all subjects who take part in this study and it might produce minor discomfort or bruising at needle sites. However, these risks are low since our laboratory technicians are experts and draw blood from large number of patients every day. In case of complications the patients will be treated appropriately, such as, they will be given cold compression for bruising, analgesic for severe pain. No compensation will be given but patients will be informed of their laboratory result.

Many patients who look normal and do not have anemic symptoms may still have low serum ferritin level. Thus it will be beneficial for patients to detect this abnormality. If it is detected that their serum ferritin level is low they will be given additional tests to find the cause, for instance, complete blood count (CBC), stool occult blood test and will be treated accordingly. This will be of great benefit to patients since some of them may have undetected underlying diseases such as carcinoma of the bowel and early detection may lead to better treatment result and longer life expectency.

Demographic data and medical information would be obtained from the medical records of patients only by personnel involved in this study. Confidentiality will be kept throughout the study including the questionnaires and information of the patients. When reporting the result no names or hospital number or any other information which may lead to the identification of the patients will be presented, thus safeguarding their rights and confidentiality further on.

This research study was approved by the Institutional Review Board of the Ethic Committee at the Faculty of Medicine, Chulalongkorn University on 19th March 2009 (Appendix A).

CHAPTER IV

RESULTS

4.1 Demographic Data - Restless legs syndrome in Parkinson's disease

Inter-observer reliability coefficient (kappa) of the interviewers was 0.783. A total of 204 PD patients were interviewed but 21 patients were excluded because of neuropathy, malignancy and history of spinal cord diseases. There were 103 males and 80 females (56.3% and 43.7% respectively).There were three out of 183 included patients (1.6%) who fulfilled the NIH-IRLSSG diagnostic criteria for RLS. Demographic variables are shown in table 1. Mean age was 63.6 ± 10.98 years in non-RLS group and 69.7 ± 9.07 years in the RLS group (p = 0.301). Mean age at onset for PD was 57.1 ± 12 years for non-RLS and 63 ± 7 years for RLS patients (p = 0.274). Both groups had a mean PD duration of 6.7 years. Mean Hoehn and Yahr (HY) stage was 2.3 ± 0.76 for non-RLS patients and 2.5 ± 1.5 for RLS patients (p = 0.764). Serum ferritin level was checked in 109 non-RLS patients and all patients with RLS. The mean values were not statistically significant (187.8 ± 167.7 ng/ml vs. 137.4 ± 91.91 ng/ml in non-RLS and RLS patients respectively, p = 0.752). Mean doses of dopaminergic medications were calculated for both non-RLS and RLS patients as follows (non-RLS, RLS, p-value): levodopa - 617.7 ± 415.3 mg/d, 633.3 ± 152.8 mg/d, 0.63, pramipexole - 1.4 ± 1.69 mg/d, 1.5 ± 1.71 mg/d, 0.796 and mean total dopaminergic medication calculated as levodopa equivalent dose (LDED)[30] - 890.75 ± 498.79 mg/d, 869.95 ± 56.2 mg/d, 0.870. Mean duration of dopaminergic medications were as follows (non-RLS, RLS, p-value): levodopa - 4.3 ± 3.7 years, 2.7 ± 0.58 years, 0.534, dopamine agonist - 2.6 ± 1.58 years, 2.5 ± 0.7 years, 0.808. None

of the variables were significantly different between PD patients with and without RLS (table 1). None of the patients interviewed had a family history of RLS.

Details of patients with RLS are given in table 2. One patient with RLS had serum ferritin level of 31.9 ng/ml (< 50 ng/ml). Her serum iron level was 41 mg/ml and iron saturation was 8.5%. This was consistent with iron deficiency. After treatment of iron deficiency her RLS symptoms resolved. Hence we attributed her RLS symptoms to be caused by iron deficiency. When excluding the patient with a ferritin level of 31.9 ng/ml (patient 1 in table 2), which may be a cause of secondary RLS (<50 ng/ml), the prevalence falls even further to 0.98%.

There were five patients who have had deep brain stimulation (DBS) surgery. None of the patients reported symptoms consistent with RLS.

Table 1. Clinical features of Parkinson's disease patients without and with RLS

		PD without RLS (n=180)	**PD with RLS (n=3)**	***p*-value**
Gender: M/F (M%/F%)		102/78 (56.7/43.3)	1/2 (33.3/66.7)	0.582
Age (years)*		63.6 ± 10.98	69.7 ± 9.07	0.301
Age at PD onset (years)*		57.1 ± 12	63 ± 7	0.274
Duration of PD (years)*		6.7 ± 5.32	6.7 ± 3.51	0.698
Hoehn & Yahr*		2.3 ± 0.76	2.5 ± 1.5	0.764
Serum Ferritin level (ng/ml)*		187.8 ± 167.7 (n = 109)	137.4± 91.91 (n = 3)	0.752
Levodopa (mg/d)*		617.7 ± 415.3	633.3 ± 152.8	0.63
Pramipexole (mg/d)*		1.4 ± 1.69	1.5 ± 1.71	0.796
Dopaminergic medication (LDED[#])*(mg/d)		890.75 ± 498.79	869.95 ± 56.2	0.870
Duration of medication (years)*	Levodopa	4.3 ± 3.7	2.7 ± 0.58	0.534
	DA[$]	2.6 ± 1.58	2.5 ± 0.7	0.808

* mean±SD, [#] LDED = levodopa equivalent dose[30],
[$]DA = dopamine agonists

Table 2. Clinical features of Parkinson's disease patients with RLS

	Patient 1	**Patient 2**	**Patient 3**
Gender	Female	Female	Male
Age (years)	66	63	80
Duration of PD (years)	3	6	10
Serum Ferritin level (ng/ml)	31.9	55	200
H&Y stage	2.5	1	4
Duration of RLS (years)	1	11	5
Onset of RLS in relation to PD	2 years after PD	5 years before PD	5 years after PD
Frequency of RLS	Daily	Almost daily	Daily
Distress caused by RLS	Moderate	Severe	Severe
Levodopa (mg/d)	1067	667	600
Pramipexole (mg/d)	-	1.25	0.375

4.2 Demographic Data - Restless legs syndrome in patients taking neuroleptic drugs

One hundred psychiatric patients taking neuroleptic drugs were interviewed. There were 51 males (51%) and 49 females (49%). Mean age was 43.44 ± 13.32 years (n=90) (table 3). Fifty-two patients (52%) were diagnosed with schizophrenia and 11 with bipolar disorder (11%). One patient had schizoaffective disorder, one had social phobia, two had anxiety, four patients had delusional disorder, seven had depression, four had depression with psychotic features, one had neurotic excoriation, two had obsessive-compulsive disorder (OCD), seven had organic psychosis and the remaining eight had psychosis which were as yet not classified into any of the diseases (table 4). Mean disease duration was 10.1 ± 8.674 years (n=97). Mean doses of neuroleptic medications are as follows (table 5): haloperidol 8.017 ± 5.8321 mg/d (n=23), perphenazine 17.11 ± 12.393 mg/d (n=35), chlorpromazine 91.67 ± 14.434 mg/d (n=3), flupixol depot 7.1 mg/d (n=1), risperidone 6.147 ± 11.8714 mg/d (n=17), clozapine 233.33 ± 144.338 mg/d (n=3), aripiprazole 12.50 ± 6.770 mg/d (n=4), quetiapine 156.25 ± 232.980 mg/d (n=10), olanzapine 10 mg/d (n=1) and ziprasidone 95.00 ± 57.446 mg/d (n=4). Mean duration of medication intake was 6.43 ± 6.02 years (n=94) (table 3).

Only one patient from 100 patients interviewed fulfilled the NIH-IRLSSG diagnostic criteria for RLS (1%). The patient was a 40 year old female who had been diagnosed with depression for seven years. She had been taking 4 mg of perphenazine for six years, 60 mg of fluoxetine for four years and one mg of lorazepam for one-and-a-half years. She described having an uncomfortable, bothersome feeling in her legs which makes her feel like wanting to amputate her legs. The symptoms started

approximately four years after starting perphenazine. These feelings would come on during periods of inactivity in the evening or at night. She had to walk around for some time to relieve her symptoms. She had these symptoms about once a week and they caused mild to moderate distress. Despite the severity of her RLS, she did not report these symptoms to her psychiatrist. She felt that the symptoms were caused by her medications so she stopped all the medications by herself. After stopping the medications the symptoms still persisted but the frequency and severity decreased. Upon follow up by telephone she admitted to still having the symtoms. She had the symptoms about three to four times in the past six months with mild severity. She denied any family history of RLS. Her blood test results are as follows: ferritin level=90.3 ng/ml, blood urea nitrogen (BUN)=7 mg/dl, creatinine=0.81 mg/dl, aspartate aminotransferase (AST)=15 U/L and alanine aminotransferase (ALT)=8 U/L.

Table 3. Demographic variables of patients taking neuroleptic drugs

	N	Mean	SD	Minimum	Maximum
Age (years)	90	43.44	13.320	18	75
Ferritin level (ng/ml)	6	315.950	206.2345	66.2	585.7
Iron level (ng/ml)	5	117.80	57.059	37	178
TIBC	5	364.80	71.671	273	472
Iron saturation (%)	5	31.2160	13.07997	13.55	49.72
Duration of medication (years)	94	6.43	6.02	1	27
Disease duration (years)	97	10.1	8.674	1	40

Table 4. Frequency of psychiatric diseases in patients taking neuroleptic drugs

Disease	N	%
Anxiety	2	2.0
Bipolar disorder	11	11.0
Delusional disorder	4	4.0
Depression	7	7.0
Major depression with psychiatric symptoms	4	4.0
Neurotic excoriation	1	1.0
OCD*	2	2.0
Organic psychosis	7	7.0
Other Psychiatric disorder	8	8.0
Schizophrenia	52	52.0
Schizoaffective disorder	1	1.0
Social phobia	1	1.0

*OCD: obsessive-compulsive disorder

Table 5. Doses of psychiatric medications (in mg/day) of patients taking neuroleptic drugs

	N	Mean	SD	Minimum	Maximum
Typical neuroleptics					
Haloperidol	23	8.017	5.8321	0.5	20.0
Perphenazine	35	17.11	12.393	2	48
Chlorpromazine	3	91.67	14.434	75	100
Flupixol depot	1	7.100	.	7.1	7.1
Atypical neuroleptics					
Risperidone	17	6.147	11.8714	0.5	37.5
Clozapine	3	233.33	144.338	150.0	400.0
Aripiprazole	4	12.500	6.7700	7.5	22.5
Quetiapine	10	156.25	232.980	12.5	800.0
Olanzapine	1	10.00	.	10.0	10.0
Ziprasidone	4	95.00	57.446	60.0	180.0
SSRI					
Fluoxetine	17	25.29	12.307	10.0	60.0
Sertraline	3	50.00	.000	50.0	50.0
Escitalopram	1	20.00	.	20.0	20.0
Fluvoxamine	1	50.00			
Benzodiazepines					
Diazepam	2	7.00	4.243	4.0	10.0
Ativan	10	2.60	3.026	1.0	10.0
Rivotril	24	2.08	1.120	0.5	4.0
Alprazolam	1	0.50	.	0.5	0.5
Tranxene	2	7.50	3.536	5.0	10.0
Tricyclic antidepressant					
Amitryptyline	5	24.10	17.6508	0.5	50.0
Anticholinergics					
Trihexyphenidyl	54	5.24	3.885	2.0	20.0

4.3 Comparison of restless legs syndrome in Parkinson's disease and restless legs syndrome in patients taking neuroleptic drugs

As the prevalence of RLS is very low in both Parkinson's disease and in patients taking neuroleptic drugs comparison between the two groups cannot be made. The prevalence of RLS in PD is 0.98% and the prevalence of RLS in patients taking neuroleptic drugs is 1%. None of the patients with RLS in both groups had a family history of RLS. Severity ranged from moderate to severe in PD group and mild to moderate in neuroleptic group.

CHAPTER V

DISCUSSIONS

5.1 Restless legs syndrome in Parkinson's disease

In our study, with patients with neuropathy, malignancy, spinal cord and end-stage renal diseases excluded, the prevalence of RLS in PD patients is 1.6%. The prevalence is much lower than the prevalence in most countries, especially the USA and Europe (3.3%-24%).[8, 11, 15, 16] When excluding the patient with a ferritin level of 31.9 ng/ml (patient 1 in table 2), which may be a cause of secondary RLS (<50 ng/ml), the prevalence falls even further to 0.98%.

As stated above, most of the previous studies have shown that the prevalence of RLS is higher in patients with PD than in comparable groups of the general population. The results of our study are not consistent with these findings.

The low prevalence of RLS in our study may be due to the following factors:

1) Our study excluded patients with conditions known to cause secondary RLS while many other studies did not.[8, 11-13] In the study of Ondo et al.[8] serum ferritin levels were significantly lower in RLS patients and in the study by Krishnan et al.[9] 50% of PD patients with RLS had serum ferritin levels <50 ng/ml and one patient had sensory neuropathy which could also cause RLS.

2) Our patients had higher levodopa and total dopaminergic medication doses than subjects in the other studies.[10-13, 15, 16] This may have masked their RLS symptoms. This may also mean that there are some ethnic influences in the amount of dopaminergic medication needed by patients to treat PD. The mean Hoehn and Yahr

(H&Y) of patients, both with and without RLS, in most studies are above 2 but less than 3 as it is in our study.[9, 10, 12, 15, 16] We cannot as yet explain how this would influence the prevalence of RLS in PD, but as it is known that genetic variants are major risk factors for RLS[31], hence there may be some genetic susceptibility that influences the prevalence of RLS in PD patients even though none of our patients with RLS had a family history of RLS.

3) There may be cultural differences in reporting symptoms. Thai patients, especially those living in the rural areas, do not usually report mild symptoms that do not disturb their quality of life or the symptoms that can be managed by their treatment regimen. Abnormal sensations may have been alleviated by walking around, moving the legs or massaging. Patients might have felt that it is not something that would be considered abnormal or something that they should report to their physician as the symptoms can go away after some manual intervention. In addition, they might have attributed their RLS symptoms to the symptoms of PD, thus underreporting the symptoms of RLS.

4) The diagnosis of RLS is exclusively based on history and there may have been recall bias which skewed the findings so that the prevalence was reported to be lower than it actually is.

There are a few studies that specifically determined the prevalence of primary RLS in PD. When comparing the results of our study to those of Nomura et al.[10] which was conducted in Japan, the prevalence of RLS in our study is much lower. The prevalence of RLS in their PD patients was 12% while it was 2.3% in their controls ($p<0.01$). Patients in their study did not have other conditions that might cause RLS and only one patient had a serum ferritin level <50 ng/ml. This prevalence is much higher than the prevalence of 0.98% in our study. The difference may be due

to lower doses of levodopa and dopamine agonists used by their patients relative to those in our study. Mean levodopa used by their patients was 510 mg/d in RLS patients and 337 mg/d in non-RLS patients while it was 633 mg/d and 617 mg/d in our patients. When converting their mean dopamine agonists doses (bromocriptine equivalent) into LDED[30] (bromocriptine x 10 = 47 mg/d in RLS and 60 mg/d in non-RLS patients) it is still lower than the mean doses of pramipexole used by our patients converted into LDED (pramipexole x 67 = 100.5 mg/d in RLS and 93.8 mg/d in non-RLS patients). Recall bias and ethnic differences also may contribute to the difference.

Our study supports the findings of the study by Calzetti et al.[15] which was done in Italy and excludes patients with causes of secondary RLS. It did not find any significant difference in the prevalence of RLS in PD patients (3.3%) when compared with controls (2.7%). Of note, as with all other studies looking at the prevalence of RLS in PD, is that PD patients are usually on levodopa or a dopamine agonist, both of which are used to treat RLS and PD. Hence the prevalence may be reported as lower than it actually is. Moreover, the diagnosis of RLS is exclusively based on history and there may be a recall bias.

Some studies report the emergence of RLS after subthalmic (STN) deep brain stimulation (DBS)[17] while others have reported a reduction of these symptoms.[18] In our study there were five patients who had undergone STN DBS. None reported RLS symptoms either prior to (retrospective interview) or after the surgery.

There was no significant difference in any of the variables between PD patients with and without RLS in contrast to other studies. Nomura et al.[10] and Peralta et al.[16] showed that PD patients with RLS were younger and had an earlier age at onset of PD when compared to PD patients who did not have RLS. Lee et al.[13] found an association between duration of antiparkinson therapy and RLS and Peralta et al.[16] found an association between doses of dopaminergic medications and RLS in their PD patients. These findings were not replicated in our study.

The definite pathophysiology of RLS is still unknown. Since the symptoms of RLS are responsive to dopaminergic medications, abnormality in the dopaminergic system has been implicated as one of the possible mechanisms. There have been studies indirectly looking at the function of the striatonigral dopaminergic system using neuroimaging techniques such as functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET) that had variable results[32]. Most of these studies found normal functioning of the presynaptic striatal dopaminergic neurons[32-34]. In a recent study by Connor et al.[35], a quantitative profile of the dopaminergic system was obtained from the substantia nigra and putamen tissue from autopsies of RLS patients and these were compared with comparable tissues of the control group. This study showed a clear pathology of the dopaminergic system suggesting cellular regulation of dopamine production that matches iron insufficiency models. Autopsy studies of RLS did not show neurodegeneration or cell loss.[35] Thus, it is possible that RLS and PD may involve a similar group of neurons but with different pathophysiology. In addition, RLS symptoms respond to opioids and anticonvulsants as well but PD symptoms do not, and PD symptoms respond to anticholinergics as

well but RLS symptoms do not.[36] This means that there must be other non-overlapping systems involved in the pathogenesis of both the diseases. This may explain why the prevalence of primary RLS in PD patients may not be higher than the prevalence of RLS in the general population even though both the diseases respond to dopaminergic medications.

The main limitation of our study is that it looks at the prevalence of RLS only in PD patients without any control group and there have been no studies looking at the prevalence of RLS in the general Thai population. Thus, we cannot definitively conclude whether this prevalence is higher than the general population or not. But looking at the prevalence of 0.98%, which excludes the secondary causes of RLS, it is lower than or about equal to the prevalence in the general population of other Asian countries[14, 37]. Therefore, it is likely that the prevalence of RLS in our study is not higher than the prevalence of RLS in the general population.

5.2 Restless legs syndrome in patients taking neuroleptic drugs

In our study, there was only one out of 100 patients taking either typical or atypical neuroleptic drugs who had fulfilled all the four cardinal features in the essential diagnostic criteria for RLS of the NIH-IRLSSG diagnostic criteria[2]. This prevalence is much lower than the prevalence in the previous study done in schizophrenic patients by Kang et al[26]. in Korea in which the prevalence of RLS in schizophrenia patients taking neuroleptics was 21.4% while it was 9.3% in the controls. In this study[26], even though patients with medical conditions known to associate with RLS were excluded from the study, serum ferritin level was not obtained in patients diagnosed as RLS. Therefore, the prevalence may be lower than

this. The reported higher prevalence of RLS in prior study may be due to inclusion of in-patients only. In our study, only out-patients were interviewed. Hence, as it can be ascribed that in-patients would have a higher disease severity than out-patients, disease severity may be one of the factors for the difference in the prevalence of both the studies. This would support the findings of the study by Kang et al.[26] that RLS could be associated with more severe psychiatric symptoms as shown by a significantly higher Brief Psychiatric Rating Scale (BPRS) score in their RLS patients compared to their non-RLS patients.

The patient with RLS in our study had serum ferritin level of 90.3 ng/ml (>50 ng/ml) and she did not have conditions which could be a secondary cause of RLS which are ESRD, liver failure, neuropathy, pregnancy and rheumatoid arthritis. Hence the patient is likely to have primary RLS or RLS from other cause. When looking carefully at the timeline of her RLS symptoms, she developed the symptoms approximately four years after taking neuroleptics. This is in contrast with previous reports of patients developing RLS soon within hours or days after starting neuroleptics or after an increase in the dosage[19-22, 24, 27]. Moreover, our patient still had symptoms a couple of months after stopping the medications. This is also inconsistent with previous reports in which the symptoms would go away in matter of hours or days after stopping the medications[19-22, 24, 27]. Hence, RLS in our patient may not have been caused by neuroleptics and the occurrence of her RLS while taking neuroleptics may be just coincidental with the symptoms rendered more severe with neuroleptic use resulting in the decrease in frequency and severity after stopping the medication. If this was the case, the prevalence of RLS in this study

would fall to 0%, indicating that RLS is not or very rarely caused by neuroleptic drug use.

Neuroimaging studies of the dopaminergic system of RLS patients have shown contradictory results. Some studies using PET and SPECT show normal striatal presynaptic dopaminergic binding[34, 38] while the others have shown reduced 18F-dopa uptake[39] though not as much as in Parkinson's disease patients. Furthermore, reduced striatal postsynaptic dopamine type 2 (D2) receptor binding was reported in some studies using ^{11}C-raclopride PET[39] and [123I] IBZM SPECT[34] scans while it was normal in some[33]. Autopsy studies of striatonigral dopaminergic system and of A11 neurons have not shown neuronal loss[35, 40]. From the abovementioned evidence, it appears that dopaminergic involvement in RLS is much more complex than just ascribing it to lack of dopamine or impaired dopamine receptor binding, or merely dopamine dysfunction. Whether RLS is either a presynaptic or postsynaptic dopaminergic disorder is unclear. Nevertheless, neuroleptics with strong D2 receptor antagonism may not cause RLS but atypical neuroleptics with weaker antagonistic activity may cause it[22, 24] (D2 and D3 are colocalised in the basal ganglia). Thus, apart from the dopaminergic system, other systems such as the opioid system, as opioids also relieve RLS symptoms, and genetic susceptibility may also play an important role in neuroleptic-induced RLS. Hence, although dopaminergic drugs provide excellent relief in symptoms of RLS, it may not be that straightforward that dopamine blocking agents should cause or precipitate RLS.

CHAPTER VI

CONCLUSIONS

6.1 Restless legs syndrome in Parkinson's disease

In conclusion, RLS and PD are different disorders but both respond very well to dopaminergic medications. Although the etiologic link comes from similar responses to dopaminergic medications, our study shows a low prevalence of RLS in PD patients. As stated in the previous chapter, the reasons for this may be due to the exclusion of patients with conditions known to cause secondary RLS, a higher dose of total dopaminergic drugs needed per day by our PD patients and ethnic and cultural differences among patients in various studies. Different pathophysiology of both the diseases may also be one of the major factors.

6.2 Restless legs syndrome in patients taking neuroleptic drugs

The prevalence of primary RLS in our study is low, which did not support the hypothesis that the state of dopamine deficiency can simply cause RLS. This evidence further suggest that the pathomechanism of dopamine responsiveness in RLS is complex and that other systems may be involved in the pathophysiology of RLS.

6.3 Limitations and Future Research

i. This study looks at the prevalence of RLS only in PD patients and patients taking neuroleptics without any control, so the prevalence of these two groups cannot be compared with the prevalence of normal Thai population. Moreover, to the best of our knowledge there has been no study looking at the prevalence

of RLS in Thai population but there are a few studies looking at the prevalence of RLS in Asian population[14, 37].

ii. There may be cultural differences in reporting the symptoms. Some people may report very mild symptoms while some may not report a more bothersome symptoms.

iii. The questionnaire which had been translated in Thai have not been properly validated. People of different socio-economic status may interpret the questions differently.

Despite these limitations our study will be useful since motor restlessness in PD patients is usually attributed to PD symptoms and in patients taking neuroleptics to akathisia. Awareness of RLS and proper management of the condition can improve the quality of life of patients.

Future researchers may validate the questionnaire and have a control population to reduce these limitations.

6.4 Research Benefits and Applications

Despite these limitations and variable findings, these studies are important since motor restlessness in PD patients is usually attributed to PD symptoms and to akathisia in patients taking neuroleptics. RLS can cause moderate to severe distress in PD patients as shown in our study, therefore attention should be paid to the symptoms and proper treatment of RLS. In cases where diagnosis of RLS is made, serum ferritin should be checked and possible causes of iron deficiency and other causes of RLS should be sought.

REFERENCES

[1] Hening W, Walters AS, Allen RP, Montplaisir J, Myers A, Ferini-Strambi L. 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 medicine. 2004 May;5(3):237-46.

[2] Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi 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 medicine. 2003 Mar;4(2):101-19.

[3] Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, et al. Restless legs syndrome prevalence and impact: REST general population study. Archives of internal medicine. 2005 Jun 13;165(11):1286-92.

[4] Allen RP, Earley CJ. The role of iron in restless legs syndrome. Mov Disord. 2007;22 Suppl 18:S440-8.

[5] Hening WA. Current guidelines and standards of practice for restless legs syndrome. The American journal of medicine. 2007 Jan;120(1 Suppl 1):S22-7.

[6] Allen RP. Restless Legs Syndrome and Periodic Limb Movements in Sleep. In: Gilman S, ed. *Neurobiology of Disease*: Elsevier 2007.

[7] Tan EK, Lum SY, Wong MC. Restless legs syndrome in Parkinson's disease. Journal of the neurological sciences. 2002 Apr 15;196(1-2):33-6.

[8] Ondo WG, Vuong KD, Jankovic J. Exploring the relationship between Parkinson disease and restless legs syndrome. Archives of neurology. 2002 Mar;59(3):421-4.

[9] Krishnan PR, Bhatia M, Behari M. Restless legs syndrome in Parkinson's disease: a case-controlled study. Mov Disord. 2003 Feb;18(2):181-5.

[10] Nomura T, Inoue Y, Miyake M, Yasui K, Nakashima K. Prevalence and clinical characteristics of restless legs syndrome in Japanese patients with Parkinson's disease. Mov Disord. 2006 Mar;21(3):380-4.

[11] Gomez-Esteban JC, Zarranz JJ, Tijero B, Velasco F, Barcena J, Rouco I, et al. Restless legs syndrome in Parkinson's disease. Mov Disord. 2007 Oct 15;22(13):1912-6.

[12] Loo HV, Tan EK. Case-control study of restless legs syndrome and quality of sleep in Parkinson's disease. Journal of the neurological sciences. 2008 Mar 15;266(1-2):145-9.

[13] Lee JE, Shin HW, Kim KS, Sohn YH. Factors contributing to the development of restless legs syndrome in patients with Parkinson disease. Mov Disord. 2009 Mar 15;24(4):579-82.

[14] Cho YW, Shin WC, Yun CH, Hong SB, Kim JH, Allen RP, et al. Epidemiology of restless legs syndrome in Korean adults. Sleep. 2008 Feb 1;31(2):219-23.

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

[16] Peralta CM, Frauscher B, Seppi K, Wolf E, Wenning GK, Hogl B, et al. Restless legs syndrome in Parkinson's disease. Mov Disord. 2009;24(14):2076-80.

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

[18] Driver-Dunckley E, Evidente VG, Adler CH, Hillman R, Hernandez J, Fletcher G, et al. Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. Mov Disord. 2006;21(8):1287-9.

[19] Wetter TC, Brunner J, Bronisch T. Restless Legs Syndrome Probably Induced by Risperidone Treatment. Pharmacopsychiatry. 2002;35(03):109-11.

[20] Kang S-G, Lee H-J, Kim L. Restless legs syndrome and periodic limb movements during sleep probably associated with olanzapine. J Psychopharmacol. 2009 July 1, 2009;23(5):597-601.

[21] Kraus T, Schuld A, Pollmacher T. Periodic Leg Movements in Sleep and Restless Legs Syndrome Probably Caused by Olanzapine. Journal of Clinical Psychopharmacology. 1999;19(5):478-9.

[22] Duggal HS, Mendhekar DN. Clozapine-Associated Restless Legs Syndrome. Journal of Clinical Psychopharmacology. 2007;27(1):89-90.

[23] Urbano MR, Ware JC. Restless Legs Syndrome Caused by Quetiapine Successfully Treated With Ropinirole in 2 Patients With Bipolar Disorder. Journal of Clinical Psychopharmacology. 2008;28(6):704-5.

[24] Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic Restless Legs Syndrome Associated With Quetiapine Use: A Case Report. Journal of Clinical Psychopharmacology. 2005;25(6):617-8.

[25] Horiguchi J, Yamashita H, Mizuno S, Kuramoto Y, Kagaya A, Yamawaki S, et al. Nocturnal eating/drinking syndrome and neuroleptic-induced restless legs syndrome (Abstract). Int Clin Psychopharmacol. 1999 Jan;14(1):33-6.

[26] Kang S-G, Lee H-J, Jung SW, Cho SN, Han C, Kim Y-K, et al. Characteristics and clinical correlates of restless legs syndrome in schizophrenia. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2007;31(5):1078-83.

[27] Khalid I, Rana L, Khalid TJ, Roehrs T. Refractory restless legs syndrome likely caused by olanzapine. J Clin Sleep Med. 2009 Feb 15;5(1):68-9.

[28] Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 1988 Jun;51(6):745-52.

[29] Allen RP, Burchell BJ, MacDonald B, Hening WA, Earley CJ. Validation of the self-completed Cambridge-Hopkins questionnaire (CH-RLSq) for ascertainment of restless legs syndrome (RLS) in a population survey. Sleep medicine. (2009);doi:10.1016/j.sleep.2008.10.007.

[30] Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. Neurology. 2008 Aug 12;71(7):474-80.

[31] Paulus W, Dowling P, Rijsman R, Stiasny-Kolster K, Trenkwalder C. Update of the pathophysiology of the Restless-Legs-Syndrome. Mov Disord. 2007;22(S18):S431-S9.

[32] Paulus W, Dowling P, Rijsman R, Stiasny-Kolster K, Trenkwalder C, de Weerd A. Pathophysiological concepts of restless legs syndrome. Mov Disord. 2007 Jul 30;22(10):1451-6.

[33] Eisensehr I, Wetter TC, Linke R, Noachtar S, Lindeiner Hv, Gildehaus FJ, et al. Normal IPT and IBZM SPECT in drug-naive and levodopa-treated idiopathic restless legs syndrome. Neurology. 2001 October 9, 2001;57(7):1307-9.

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

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

[36] Moller JC, Unger M, Stiasny-Kolster K, Oertel WH. Restless Legs Syndrome (RLS) and Parkinson's disease (PD)-Related disorders or different entities? Journal of the neurological sciences. 2009 Sep 13;doi:10.1016/j.jns.2009.08.035.

[37] Tan EK, Seah A, See SJ, Lim E, Wong MC, Koh KK. Restless legs syndrome in an Asian population: A study in Singapore. Mov Disord. 2001 May;16(3):577-9.

[38] Claudia T, Arthur SW, Wayne AH, Sudhansu C, Angelo A, Vijay D, et al. Positron emission tomographic studies in restless legs syndrome. Mov Disord. 1999;14(1):141-5.

[39] Turjanski N, Lees AJ, Brooks DJ. Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies. Neurology. 1999 March 1, 1999;52(5):932-.

[40] Earley CJ, Allen RP, Connor JR, Ferrucci L, Troncoso J. The dopaminergic neurons of the A11 system in RLS autopsy brains appear normal. Sleep Med. 2009 Dec;10(10):1155-7.

APPENDICES

Appendix A

Approval by the Institutional Review Board of Ethic Committee of Faculty of Medicine, Chulalongkorn University

COA No. 213/2009
IRB No. 518/51

INSTITUTIONAL REVIEW BOARD
Faculty of Medicine, Chulalongkorn University
1873 Rama 4 Road, Patumwan, Bangkok 10330, Thailand, Tel 662-256-4455 ext 14, 15

Certificate of Approval

The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, has approved the following study which is to be carried out in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Report, CIOMS Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP)

Study Title : The Prevalence of Restless Legs Syndrome in Thai patients with Parkinson's Disease and Patients Neuroleptic Drugs

Study Code : -

Study Center : Chulalongkorn University

Principal Investigator : Dr.Priya Jagota

Document Reviewed :

1. Protocol
2. Information Sheet for Volunteers and Consent Form
3. Case Report Form

Signature: ..... **Signature:** .....
(Emeritus Professor Anek Aribarg, M.D.)
Chairman of
The Institutional Review Board

(Associate Professor Sopit Thamaree)
Committee and Secretary of
The Institutional Review Board

Date of Approval : March 19, 2009

Approval Expire Date : March 19, 2010

Approval is granted subject to the following conditions: (see back of this Certificate)

Appendix B
Information Sheet for Volunteers and Consent Form
ข้อมูลคำอธิบายสำหรับผู้เข้าร่วมการศึกษาวิจัย

หัวข้อการวิจัย: **ความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต**

แพทย์ผู้ทำการวิจัย

พญ. ปรียา จาโกต้า หน่วยประสาทวิทยา ภาควิชาอายุรศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย เบอร์โทรศัพท์ 0817105516	**รองศาสตราจารย์นายแพทย์ รุ่งโรจน์ พิทยศิริ** อาจารย์ที่ปรึกษาวิทยานิพนธ์ ภาควิชาอายุรศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ฝ่ายวิจัยคณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย อาคารอานันทมหิดล ชั้น3 เบอร์โทรศัพท์ 0-2256-4454 / 0-2256-4493	**ผู้ช่วยศาสตราจารย์นายแพทย์ ธนินทร์ อัศววิเชียรจินดา** อาจารย์ที่ปรึกษาวิทยานิพนธ์ (ร่วม) ภาควิชาอายุรศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

1. **คำชี้แจงเกี่ยวกับการวิจัย**

กลุ่มอาการขาอยู่ไม่สุข เป็นกลุ่มอาการที่ทำให้เกิดความทุกข์ทรมานได้มาก สามารถพบร่วมกับโรคอื่นๆ ได้ เช่น ไตวาย, โรคซีดจากการขาดธาตุเหล็ก ในต่างประเทศได้มีการศึกษาหาความสัมพันธ์และความชุกในคนปกติและผู้ป่วยโรคต่างๆ พบว่าสาเหตุสำคัญของการเกิดกลุ่มอาการนี้คือ การขาดธาตุเหล็ก ซึ่งผู้ป่วยจะมีระดับเฟริติน (ferritin) ต่ำ อีกส่วนหนึ่งเชื่อว่าเป็นกรรมพันธุ์ กลไกของกลุ่มอาการเชื่อว่าเกิดจากขาดสารโดปามีนซึ่งเป็นกลไกที่คล้ายกันกับโรคพาร์กินสัน การรับประทานยาในกลุ่มรักษาโรคจิต (neuroleptic) ออกฤทธิ์ยับยั้งสารโดปามีน จึงมีความเป็นไปได้ว่าอาจพบกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยสองกลุ่มนี้มากกว่าประชากรทั่วไป ในประเทศไทยยังไม่มีการศึกษาหาความชุกของกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยทั้งสองกลุ่ม

2. **วัตถุประสงค์ของการศึกษาวิจัย** มีดังนี้

a. หาความชุกและความรุนแรงของกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต
b. ศึกษาความชุกของผู้ป่วยกลุ่มอาการขาอยู่ไม่สุขในทั้ง 2 กลุ่มที่มีสมาชิกในครอบครัวมีกลุ่มอาการขาอยู่ไม่สุขด้วย
c. หาความสัมพันธ์ระหว่างระดับเฟริติน ในเลือดและการเกิดกลุ่มอาการขาอยู่ไม่สุขในผู้ป่วยทั้งสองกลุ่ม
d. เปรียบเทียบข้อมูลข้างต้นในผู้ป่วยทั้ง 2 กลุ่ม
e. สามารถนำแบบสอบถามที่สมบูรณ์แล้วมาหาความชุกของกลุ่มอาการขาอยู่ไม่สุขในประชากรไทยได้ในอนาคต

3. <u>วิธีการวิจัย</u>

ในการศึกษาวิจัยต้องการอาสาสมัครที่เป็นโรคพาร์กินสันจำนวน 200 คน และอาสาสมัครที่รับประทานยากลุ่มยารักษาโรคจิตจำนวน 200 คน อาสาสมัครทุกท่านที่ตัดสินใจเข้าร่วมในโครงการศึกษาวิจัยจะได้รับการเจาะเลือดปริมาณ 4 มล. สำหรับการตรวจระดับเฟริติน จำนวน 1 ครั้ง

การตรวจดังกล่าวข้างต้นได้รับสนับสนุนจากกองทุนการวิจัย อาสาสมัครไม่ต้องเสียค่าใช้จ่ายใดๆทั้งสิ้นในการตรวจเลือดนี้ ไม่มีกระบวนการพยาบาลอื่นๆ หรือการนัดติดตามผลหลังจากการตรวจเลือด ผลการตรวจเลือดจะถูกบันทึก วิเคราะห์ และหาความสัมพันธ์ระหว่างประวัติของผู้ป่วย การวินิจฉัยโรคและบันทึกทางการแพทย์โดยผู้ค้นคว้าวิจัย พยาบาลวิจัย และนักสถิติ

4. <u>ประโยชน์ที่ได้รับจากการวิจัย</u>

อาสาสมัครจะไม่ได้รับค่าตอบแทนใดๆจากการเข้าร่วมโครงการวิจัย ผลเลือดจะถูกแจ้งให้อาสาสมัครทราบเมื่ออาสาสมัครต้องการทราบผลการตรวจเลือด หรือ เมื่อผลการตรวจเลือดผิดปกติที่อาจมีผลกระทบต่อการรักษาโรคของอาสาสมัคร ผลการศึกษาวิจัยในครั้งนี้จะเป็นประโยชน์ต่อผู้ป่วยในปัจจุบันและผู้ป่วยในอนาคต โดยจะได้ข้อมูลของความชุกของโรคขาอยู่ไม่สุขในคนไทยที่เป็นโรคพาร์กินสันและผู้ป่วยไทยที่รับประทานยากลุ่มยารักษาโรคจิต อีกทั้งสามารถนำแบบสอบถามมาใช้หาความชุกของกลุ่มอาการขาอยู่ไม่สุขในประชากรทั่วไปได้ในอนาคต

5. <u>ความเสี่ยงและความไม่สะดวกสบาย</u>

เมื่อมีการเจาะเลือดสำหรับการตรวจทางห้องปฏิบัติการ ท่านอาจได้รับความเจ็บปวดบ้าง มีเลือดออกเล็กน้อยหรือรอยช้ำที่บริเวณที่เจาะด้วยเข็ม หากเกิดภาวะแทรกซ้อนหรืออันตราย ท่านจะได้รับการรักษาตามมาตรฐานวิชาชีพแพทย์

6. <u>คำชี้แจงเกี่ยวกับสิทธิของผู้ป่วยและอาสาสมัคร</u>

ผู้ป่วยมีสิทธิที่จะปฏิเสธการเข้าร่วมการศึกษาวิจัย โดยยังมีสิทธิที่จะได้รับการดูแลจากแพทย์ตามปกติ ผู้ป่วยหรืออาสาสมัครมีสิทธิที่จะถอนตัวจากการวิจัยครั้งนี้เมื่อไรก็ได้ แม้ว่าท่านจะได้ลงนามในการวิจัยแล้ว โดยท่านจะไม่ได้รับผลเสียใดๆทั้งสิ้น และข้อมูลส่วนตัวของท่านจะไม่ถูกบันทึกเพิ่มเติม

7. <u>การปกปิดเป็นความลับ</u>

ข้อมูลที่อาจนำไปสู่การเปิดเผยตัวของท่าน จะได้รับการปกปิดและไม่เปิดเผยต่อสาธารณชน ในกรณีที่ผลการวิจัยได้รับการตีพิมพ์ ชื่อและที่อยู่ของท่านจะได้รับการปกปิดเสมอ โดยจะใช้เฉพาะรหัสโครงการวิจัยของท่านเท่านั้น

จากการยินยอมลงนามของท่าน แพทย์ผู้วิจัยสามารถเข้าไปทำการตรวจสอบบันทึกข้อมูลทางการแพทย์ของท่านได้ตลอดเวลาแม้จะสิ้นสุดโครงการวิจัยไปแล้วก็ตาม หากท่านต้องการยกเลิกการใช้สิทธิดังกล่าว ท่านสามารถเขียน

บันทึกขอยกเลิกการให้คำยินยอม โดยส่งไปที่ พญ. ปรียา จาโกต้า หน่วยประสาทวิทยา ภาควิชาอายุรศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ขอบคุณในการร่วมมือของท่านมา ณ ที่นี้

ใบยินยอมเข้าร่วมการวิจัย

วันที่ :…… **ชื่อ-นามสกุล:.....**

HN: ..... **เบอร์โทรศัพท์.....**

หัวข้อการวิจัย: **ความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต**

ข้าพเจ้าได้อ่านและมีความเข้าใจข้อมูลที่อยู่ในเอกสารข้างต้นและได้รับโอกาสในการพิจารณา และถามคำถามเกี่ยวกับข้อมูลที่เกี่ยวข้องกับการมีส่วนร่วมในการศึกษานี้ของข้าพเจ้า ข้าพเจ้าได้พูดคุยโดยตรงกับแพทย์และได้รับคำตอบต่อทุกคำถามจนข้าพเจ้าพอใจ ข้าพเจ้าได้รับสำเนาเอกสารให้คำยินยอมนี้ 1 ฉบับ ข้าพเจ้าสมัครใจและยินยอมเข้าร่วมโครงการศึกษานี้โดยการตรวจทางห้องปฏิบัติการที่กล่าวข้างต้น การวิเคราะห์ผลเลือด และการเก็บข้อมูลประวัติการรักษาของข้าพเจ้า

ข้าพเจ้าอนุญาตให้เปิดเผยข้อมูลในบันทึกทางการแพทย์ (ข้อมูลที่รวบรวมจากการเข้าร่วมการศึกษานี้) สำหรับการยื่นต่อหน่วยงานกำกับดูแลของรัฐหรือหน่วยงานอื่นๆ ของรัฐ และสำหรับการตีพิมพ์ที่อาจเกิดขึ้นโดยแพทย์ผู้วิจัยหรือผู้ร่วมงานของแพทย์ ข้อมูลบันทึกทางการแพทย์อาจถูกตรวจสอบจากหน่วยงานของรัฐหรือคณะกรรมการจริยธรรม แต่อย่างไรก็ตาม การถือเป็นความลับจะถูกนำมาปฏิบัติ เพื่อให้ชื่อไม่ถูกระบุในหน่วยงานต่างๆ ของการศึกษานี้

ผู้ให้ความยินยอม:

_____	_____	_____
ลายเซ็น	ชื่อ	วันที่

พยาน หรือผู้แทนโดยชอบธรรม:

(เฉพาะที่เกี่ยวข้อง)	_____ ลายเซ็นพยาน/ผู้แทนโดยชอบธรรม	_____ ชื่อพยาน /ผู้แทนโดยชอบธรรม	_____ วันที่
(เฉพาะที่เกี่ยวข้อง)	_____ ลายเซ็นพยาน/ผู้แทนโดยชอบธรรม	_____ ชื่อพยาน /ผู้แทนโดยชอบธรรม	_____ วันที่

แพทย์ผู้ลงนามวิจัย:

_____	_____	_____
ลายเซ็นแพทย์	ชื่อแพทย์	วันที่

ในกรณีที่ผู้เข้าร่วมโครงการไม่สามารถเขียนชื่อได้ ให้ลงนามโดยวิธีประทับลายนิ้วมือแทน และขอให้ผู้แทนโดยชอบธรรมหรือพยาน 2 คน ที่ไม่เกี่ยวข้องกับผู้วิจัยเป็นผู้รับรองด้วย

Appendix C
Case Report Form
แบบบันทึกข้อมูล

<u>ความชุกของกลุ่มอาการขาอยู่ไม่สุข ในผู้ป่วยไทยที่เป็นโรคพาร์กินสันและผู้ป่วยที่รับประทานยารักษาโรคจิต</u>

1. Code No. .....
2. อายุ .....
3. เพศ ☐ ชาย
   ☐ หญิง จำนวนการตั้งครรภ์.....
   จำนวนการแท้ง.....
   จำนวนบุตร.....

4. ระดับการศึกษาสูงสุด
   ☐ 1. ไม่ได้รับการศึกษา ☐ 2. ประถมศึกษา
   ☐ 3. มัธยมศึกษาตอนต้น ☐ 4. มัธยมศึกษาตอนปลายหรือเทียบเท่า (ปวช.)
   ☐ 5. อนุปริญญาหรือเทียบเท่า (ปวส.) ☐ 6. ปริญญาตรีหรือสูงกว่า

5. ท่านดื่มสุราหรือไม่ ☐ ไม่
   ☐ ดื่มเป็นครั้งคราว (< 1 ครั้ง/สัปดาห์) ระบุ.....ครั้ง/เดือน
   ☐ ดื่มเป็นประจำ……ครั้ง/สัปดาห์

6. ท่านสูบบุหรี่หรือไม่ ☐ ไม่
   ☐ เคยสูบบุหรี่ เคยสูบ .....มวนต่อวัน.เป็นเวลา.....ปี (.....pack*years)
   แต่เลิกสูบมา……ปี
   ☐ ยังสูบบุหรี่อยู่ จำนวน.....มวนต่อวัน จำนวนปีที่สูบ.....ปี (.....pack*years)

7. ท่านมีโรคประจำตัวหรือไม่
   ☐ ไม่
   ☐ ใช่
   ได้แก่ ☐ โรคเลือด
   ☐ โรคซีดจากการขาดธาตุเหล็ก
   ☐ โรคซีดชนิดอื่น.....
   ☐ โรคโลหิตชนิดอื่น.....
   เป็นมา.....ปี
   ☐ โรคทางจิตเวช ได้แก่.....
   เป็นมา.....ปี
   ☐ โรคไตวาย (E)

☐ โรคพาร์กินสัน

เป็นมา.....ปี

(เฉพาะแพทย์) **MODIFIED HOEHN AND YAHR STAGING**

- ☐ 0 = No sign of disease
- ☐ 1 = Unilateral disease
- ☐ 1.5 = Unilateral plus axial involvement
- ☐ 2 = Bilateral disease
- ☐ 2.5 = Mild bilateral disease with recovery on pull test
- ☐ 3 = Mild to moderate bilateral disease, some postural instability, physically independent
- ☐ 4 = Severe disability, still able to walk or stand unassisted
- ☐ 5 = Wheelchair bound or bedridden unless aided

☐ โรคปลายประสาทเสื่อม(Peripheral Neuropathy) (E)

☐ เบาหวาน เป็นมา.....ปี

☐ โรคกระดูกสันหลังทับเส้นประสาทหรือโรคทางกระดูกสันหลังโรคอื่น (E)

☐ อื่นๆ ได้แก่.....

เป็นมา.....ปี

8. ขณะทำแบบทดสอบท่าน

	ไม่ใช่	ใช่
8.1 กำลังตั้งครรภ์	☐	☐ (E)
8.2 มีภาวะติดเชื้อ, มีไข้	☐	☐ (เจาะเลือดครั้งต่อไป)

9. ท่านรับประทานยาเป็นประจำหรือไม่ ☐ ไม่ ☐ ใช่

ถ้าตอบว่า ใช่ ยาที่ท่านรับประทานอยู่คือ 1.....ระยะเวลา.....ปี

2.....ระยะเวลา.....ปี

3.....ระยะเวลา.....ปี

4.....ระยะเวลา.....ปี

5.....ระยะเวลา.....ปี

10. ท่านมีสมาชิกในครอบครัวเป็น “กลุ่มอาการขาอยู่ไม่สุข” หรือไม่ ☐ ไม่มี ☐ มี

(หรือมีอาการตามแบบสอบถาม) ถ้ามีโปรดระบุ.....

11. ท่านเคยหรือกำลังรักษา“กลุ่มอาการขาอยู่ไม่สุข” หรือไม่ ☐ ไม่มี ☐ ใช่

11. ระดับ Ferritin ในเลือด .....ng/ml

ระดับ Fe ในเลือด (optional) .....mg/ml

ระดับ TIBC ในเลือด (optional) ..... %

คำนวณค่า Iron saturation ได้ (optional) ..... %

NOTE: E = exclusion criteria

Appendix D
(Thai version of the Cambridge-Hopkins Restless Legs Syndrome Short Form 2 Diagnostic Questionnaire (RLS-SFDQ13))

แบบสอบถามกลุ่มอาการขาอยู่ไม่สุข สถาบัน แคมบริดจ์-ฮ๊อพกิ้นส์ (RLS – SFDQ13)

กรุณาอ่านเอกสารข้อมูล ก่อนจะตกลงร่วมมือในการตอบแบบสอบถามนี้และโปรดทราบว่ามีที่อยู่ติดต่อได้สำหรับคำแนะนำและข้อมูลเพิ่มเติม การแบบสอบถามนี้ถือเป็นความสมัครใจของท่านทั้งสิ้น ข้อมูลทั้งหมดถือเป็นความลับและจะไม่มีการเปิดเผยข้อมูลใดๆที่บ่งชี้ถึงตัวท่านต่อบุคคลอื่นนอกเหนือจากเจ้าหน้าที่วิจัยที่ทำงานในโครงการนี้(เท่านั้น) คำตอบจากแบบสอบถามนี้จะไม่ถูกบันทึกลงในประวัติทางการแพทย์

กรุณา วงกลม คำตอบที่ตรงกับท่านมากที่สุด :

1. ท่านมี หรือ เคยมี ความรู้สึกไม่สบายขาหรือมีการรับรู้ผิดปกติที่ขา เป็นๆ หายๆในเวลานั่งหรือนอนหรือไม่ ?	• ใช่ • ไม่ใช่
2. ท่านมี หรือ เคยมี ความรู้สึกอยากหรือจำเป็นต้องขยับขา เป็นๆ หายๆ ในเวลานั่งหรือนอนหรือไม่ ?	• ใช่ • ไม่ใช่

ถ้าคำตอบของท่าน คือ ใช่ อย่างน้อยหนึ่งข้อ กรุณาตอบคำถามในตอน ก และ ตอน ข

ตอน ก: แบบสอบถามเกี่ยวกับความรู้สึกดังกล่าวข้างต้น

3. ท่านมักจะมีความรู้สึกเหล่านี้เวลาพัก (ไม่ว่าจะนั่งหรือนอน) หรือเวลาเคลื่อนไหว ?	• ขณะพัก • ขณะเคลื่อนไหว
4. ความรู้สึกเหล่านี้ดีขึ้นหรือไม่ ถ้าท่านได้ลุกขึ้นหรือขณะมีการเคลื่อนไหว?	• ใช่ • ไม่ใช่ • ไม่ทราบ
5. ความรู้สึกเหล่านี้ มักจะเกิดขึ้นในช่วงเวลาใดของวัน ? *(สามารถวงกลมได้มากกว่าหนึ่งข้อ)*	• เช้า • กลางวัน • บ่าย • เย็น • กลางคืน • เท่ากัน ทุกเวลา
6. การเปลี่ยนท่าที่ขาเพียงหนึ่งครั้ง โดยไม่มีการขยับขาต่อสามารถช่วยผ่อนคลายความรู้สึกเหล่านี้ได้หรือไม่?	• ช่วยผ่อนคลาย • ไม่ได้ช่วยผ่อนคลาย • ไม่ทราบ
7 ก. ความรู้สึกเหล่านี้เคยเกิดจากตะคริวที่ขาหรือไม่ ?	• ใช่ • ไม่ใช่ • ไม่ทราบ
7 ข. ถ้า ใช่ มันเกิดจากตะคริวที่ขาทุกครั้งหรือไม่ ?	• ใช่ • ไม่ใช่ • ไม่ทราบ
8. ความรู้สึกเหล่านี้เกิดขึ้นเฉพาะ เมื่อท่านอยู่ในท่านั่งหรือท่านอนเท่านั้น	• ไม่ • เฉพาะเวลานั่ง • เฉพาะเวลานอน • ทั้งในเวลานั่งและนอน
9. ในขณะที่มีความรู้สึกเหล่านี้ที่ขาของท่าน ท่านรู้สึกทุกข์ทรมานมากน้อยเพียงใด ?	• ไม่รู้สึกเลย • รู้สึกเล็กน้อย • รู้สึกปานกลาง • รู้สึกอย่างมาก

มีต่อด้านหลัง

10. ในเวลา 12 เดือนที่ผ่านมา ท่านมีความรู้สึกเหล่านี้ที่ขาของท่าน บ่อยแค่ไหน ? (กรุณาวงกลมเพียงข้อเดียว)	• ทุกวัน • 4-5 วันต่อสัปดาห์ • 2-3 วันต่อสัปดาห์ • 1 วันต่อสัปดาห์ • 2 วันต่อเดือน • 1 วันต่อเดือนหรือน้อยกว่า • ไม่เคย
11. ท่านเริ่มสังเกตพบความรู้สึกเหล่านี้ที่ขาของท่าน เมื่อท่านอายุเท่าใด? (โปรดระบุอายุ)	_____ ปี

ตอน ข

12. ท่านจะบรรยายความรู้สึกเหล่านี้อย่างไร	_____
13. **(สำหรับผู้ป่วยพาร์กินสัน)** ความรู้สึกเหล่านี้ เริ่มก่อนหรือหลังอาการโรคพาร์กินสัน	☐ ก่อน _____ ปี ☐ หลัง _____ ปี
14. **(สำหรับผู้ป่วยที่ทานยาจิตเวช)** ความรู้สึกเหล่านี้ เริ่มก่อนหรือหลังทานยาจิตเวช	☐ ก่อน _____ ปี ☐ หลัง _____ ปี

Appendix E

Example of abnormal sensations

ตัวอย่างคำศัพท์อธิบายความรู้สึกผิดปกติที่ขา

ความรู้สึกว่ามีแมลงกำลังไต่อยู่
ความรู้สึกว่ามีมดกำลังไต่อยู่
รู้สึกประหม่าอย่างมาก
รู้สึกกระตุก
รู้สึกมีหนอนไต่
รู้สึกว่ามีไฟช๊อตอยู่ในหลอดเลือด
รู้สึกว่ามีไฟช๊อต
รู้สึกช๊อค
เจ็บปวด
รู้สึกว่าต้องขยับ
รู้สึกไหม้
รู้สึกขาบีบเกร็ง
กลัวสุดขีด
รู้สึกถึงการฉีก
รู้สึกเต้นเป็นจังหวะ
รู้สึกแน่น
รู้สึกจับทันที
รู้สึกขากระตุกอย่างเร็ว
รู้สึกว่าคันตามกระดูก
รู้สึกขาผิดปกติ
รู้สึกว่าขาเคลื่อนไหวไม่สบาย

***Translated from**: 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. Table 2. Sleep Medicine 4 (2003) 101-119*

Appendix F

English version of the questionnaire

Cambridge- Hopkins Restless Legs Syndrome
Short Form 2 DIAGNOSITC QUESTIONNAIRE
(RLS-SFDQ13)

Please read the Information Sheet before consenting to participate by completing the questionnaire and note that there are contact details available for further information and advice. This questionnaire is completely voluntary,. All information obtained will be confidential and no information identifying you will be released to anyone other than the research staff working on this project. Nothing you say on the questionnaire will be added to your medical records.

Answer the questions as completely as you can. Please ***circle*** *the one best answer to each question* thus: ☐

1. Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?	• Yes • No
2. Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?	• Yes • No

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If you answered YES to either question continue with Section A (Question 3).

Section A: this section is about these feelings

3. Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active?	☐ Resting ☐ Active
4. If you get up or move around when you have these feelings do these feelings get any better while you actually keep moving?	☐ Yes ☐ No ☐ Don't know
5. Which times of day are these feelings in your legs **most** likely to occur? *(Please circle one or more than one)*	☐ Morning ☐ Mid-day ☐ Afternoon ☐ Evening ☐ Night ☐ About equal at all times
6. Will simply changing leg position by itself *once* without continuing to move usually relieve these feelings?	☐ Usually relieves ☐ Does *not* usually relieve ☐ Don't know

7a. Are these feelings *ever* due to muscle cramps?	☐ Yes ☐ No ☐ Don't know
7b. If so, are they *always* due to muscle cramps?	☐ Yes ☐ No ☐ Don't know
8. Do these feelings occur *only* when sitting or only when lying down?	☐ Neither ☐ Only when sitting ☐ Only when lying down ☐ Both when sitting and . when lying down.
9. When you actually experience the feelings in your legs, how *distressing* are they?	☐ Not at all distressing ☐ A little bit ☐ Moderately ☐ Extremely distressing
10 In the past 12 months, how often did you experience these feelings in your legs? (please circle only one answer)	☐ Every day ☐ 4-5 days per wk ☐ 2-3 days per wk ☐ 1 day per wk ☐ 2 days per month ☐ 1 day per month or less ☐ Never

11. Approximately how old were you when you first noticed these feelings in your legs?(*please write age)*	☐☐ Yrs

AUTHOR'S BIOGRAPHY

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Date of Birth

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Education

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