The Low Prevalence of Primary Restless Legs Syndrome in Thai Parkinson's Disease Patients at Chulalongkorn University Hospital

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Objective: *There have been many studies of the prevalence of restless legs syndrome (RLS) in Parkinson's disease (PD). Some studies found a lower prevalence than in comparable groups in the general population while others reported more RLS. The present study was designed to determine the prevalence of primary RLS in Thai PD patients.*
Material and Method: *PD patients were interviewed for RLS symptoms and were excluded if they had a malignancy, end-stage renal disease, neuropathy, a history of spinal cord diseases or were pregnant. Serum ferritin levels were measured.*
Results: *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%. None of the following variables were significantly different in patients with and without RLS: age, gender, age at onset of PD, duration of PD, Hoehn and Yahr stage, serum ferritin level and dose and duration of dopaminergic medication. None of the patients who have had subthalamic nucleus deep brain stimulation (n = 5) had RLS.*
Conclusion: *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.*

Keywords: *Parkinson's disease, Restless legs syndrome*

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Parkinson's disease (PD) is a neuro-degenerative disorder while restless legs syndrome (RLS) does not fit this category. However, the fact that both respond to dopaminergic therapy suggests that there may be an etiologic link between these two disorders. Previous prevalence studies have shown that RLS is more prevalent in Caucasians[1,2] but occurs less in people of Asian origin[3]. Despite these differences most of the prevalence studies have shown that RLS is more common in patients with Parkinson's disease (PD) than in the general population regardless of their ethnic origin[4-8]. PD is a distressing disorder, RLS may cause additional distress in these patients. The authors sought to determine the prevalence, severity, and family history of RLS in Thai patients with PD. In addition, the authors studied the differences in serum ferritin levels of PD patients with and without RLS.

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Material and Method

The present study was approved by the Ethics Committee of the Chulalongkorn University Hospital. PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria[9]. PD patients were consecutively enrolled from the Out-Patient Movement Disorders Clinic of Chulalongkorn University Hospital. Patients were interviewed by a neurologist trained in movement disorders or a clinically trained interviewer. The Cambridge-Hopkins Diagnostic Questionnaire for RLS (CH-RLSq)[10] was translated into Thai (and back-translated into English) by a certified translator to serve as a guide for structured interviews. Diagnosis of RLS was made if the symptoms fulfilled all the four

essential diagnostic criteria for RLS of the National Institute of Health-International Restless Legs Syndrome Study Group (NIH-IRLSSG)[11]. Those who were interviewed by a trained interviewer and were positive for RLS, or when the diagnosis was uncertain, were examined again by one of the authors of the present study. Careful history was taken to distinguish between symptoms of "wearing-off" and symptoms of RLS.

Patients were included in the present study only if they were 18 years old or above and gave their informed consent. Exclusion criteria included history of any kind of malignancies, end-stage renal disease, neuropathy, history of spinal cord diseases and pregnancy. Patients with a malignancy were excluded since many chemotherapy drugs can cause drug-induced neuropathy. Patients were interviewed for the above conditions and a clinical examination was done in suspected cases. Patients who were not able to give reliable information also were excluded. Serum ferritin levels were determined in subjects who gave informed consent for the test.

Levodopa equivalent dose for dopaminergic drugs were calculated as follows[12]: levodopa (LD) (mg) + pramipexole (mg) x 67 + LD (mg) x 1/3 if on entacapone + LD (mg) x 1.2 if taking 10 mg of selegiline + LD (mg) x 1.1 if taking 5 mg of selegiline + benzhexol (mg) x 31 + bromocriptine (mg) x 10 + piribedil (mg) x 1.67.

Statistical analysis

Categorical data were analyzed by using frequency distributions and percentages. Statistical analysis was performed in SPSS version 17.0 (SPSS Inc., Chicago, Ill). Continuous data were analyzed by using mean values and the standard deviations (SD). The data had a non-normal distribution so statistical differences were analyzed by Mann-Whitney U test. Inter-observer reliability was analyzed using the Kappa test.

Results

Inter-observer reliability coefficient (kappa) was 0.783. A total of 204 PD patients were interviewed but 21 patients were not included in accordance with the exclusion criteria. There were 103 males and 80 females (56.3% and 43.7% respectively).Three out of 183 included patients (1.6%) fulfilled the NIH-IRLSSG diagnostic criteria for RLS. None of the patients had been diagnosed with RLS before the present study. Demographic variables are shown in Table 1. None of the variables were significantly different between PD patients with and without RLS.

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

	PD without RLS (n = 180)	PD with RLS (n = 3)
Gender: M/F (M%/F%)	102/78 (56.7/43.3)	1/2 (33.3/66.7)
Age (years)*	63.6 ± 10.98	69.7 ± 9.07
Age at PD onset (years)*	57.1 ± 12	63 ± 7
Duration of PD (years)*	6.7 ± 5.32	6.7 ± 3.51
Hoehn & Yahr (H&Y)*	2.3 ± 0.76	2.5 ± 1.5
H&Y stage 1	15	1
H&Y stage 1.5	15	0
H&Y stage 2	31	0
H&Y stage 2.5	68	1
H&Y stage 3	15	0
H&Y stage 4	8	1
H&Y stage 5	2	0
Serum Ferritin level (ng/ml)*	187.8 ± 167.7 (n = 109)	137.4 ± 91.91 (n = 3)
Levodopa (mg/d)*	617.7 ± 415.3	633.3 ± 152.8
Pramipexole (mg/d)*	1.4 ± 1.69	1.5 ± 1.71
Dopaminergic medication (LDED#)*(mg/d)	890.75 ± 498.79	869.95 ± 56.2
Duration of medication (years)*		
Levodopa	4.3 ± 3.7	2.7 ± 0.58
DA	2.6 ± 1.58	2.5 ± 0.7

* Mean ± SD

LDED = levodopa equivalent dose (12)

Table 2. Clinical features of PD 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)	1,067	667	600
Pramipexole (mg/d)	-	1.25	0.375

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 < 50 ng/ml and iron saturation of 8.5% (normal: >15%) which is consistent with iron deficiency. After treatment with ferrous sulphate, her RLS symptoms significantly improved. There were five patients who have had deep brain stimulation (DBS) surgery but none of these patients reported symptoms consistent with RLS.

Discussion

In the present 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%)[5,7,13,14]. 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%.

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

1) The present study excluded patients with conditions known to cause secondary RLS while many other studies did not[5,7,8,15]. In the study of Ondo et al[7] serum ferritin levels were significantly lower in RLS patients and in the study by Krishnan et al[6] 50% of PD patients with RLS had serum ferritin levels < 50 ng/ml and one patient had sensory neuropathy.

2) Patients in the present study had higher levodopa and total dopaminergic medication doses than subjects in other studies[4,5,8,13-15]. 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 as 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 the present study at Chulalongkorn University Hospital[4,6,8,13,14]. The authors 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[16], hence there may be some genetic susceptibility that influences the prevalence of RLS in PD patients.

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.

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 the present study to those of Nomura et al[4] which was conducted in Japan, the prevalence of RLS in the present 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 the present study. The difference may be due to lower doses of levodopa and dopamine agonists used by their patients relative to those in the present 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 the presented patients. When converting their mean dopamine agonists

doses (bromocriptine equivalent) into LDED[12] (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 the presented 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.

The present study supports the findings of the study by Calzetti et al[14] 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 when compared with controls. 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 the present 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[4] and Peralta et al[13] 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[15] found an association between duration of antiparkinson therapy and RLS and Peralta et al[13] found an association between doses of dopaminergic medications and RLS in their PD patients. These findings were not replicated in the present 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[19]. Most of these studies found normal functioning of the presynaptic striatal dopaminergic neurons[19-21]. In a study by Connor et al[22], 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. The present 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[22]. 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[23]. This supports that there are other non-overlapping systems involved in the pathogenesis of both diseases. This may explain why the prevalence of primary RLS in PD patients may not be high even though both diseases respond to dopaminergic medications.

The main limitation of the present 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 a Thai population. Thus, the authors cannot definitely 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[3,24]. Therefore, it is likely that the prevalence of RLS in the present study is not higher than the prevalence of RLS in the general population.

Despite these limitations and variable findings, these studies are important since motor restlessness in PD patients is usually attributed to PD symptoms. RLS can cause moderate to severe distress in PD patients as shown in the present 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.

Conclusion

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, the present study shows a low prevalence of RLS in PD patients. As stated above, the reasons for this result

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 the presented PD patients and ethnic and cultural differences among patients in various studies. Different pathophysiology of both diseases may also be one of the major factors.

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Potential conflicts of interest

None.

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ความชุกของโรคขาอยู่ไม่สุขในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน

ปรียา จาโกต้า, ธนินทร์ อัศววิเชียรจินดา, รุ่งโรจน์ พิทยศิริ

วัตถุประสงค์: *มีการศึกษาถึงความชุกของโรคขาอยู่ไม่สุขในผู้ป่วยโรคพาร์กินสันหลายการศึกษา บางการศึกษาพบว่าความชุกของโรคขาอยู่ไม่สุขในผู้ป่วยโรคพาร์กินสันน้อยกว่าความชุกในประชากรทั่วไป แต่บางการศึกษาพบว่ามีความชุกมากกว่า งานวิจัยนี้ต้องการศึกษาหาความชุกของโรคขาอยู่ไม่สุขในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน*

วัสดุและวิธีการ: *ทำการวิจัยโดยการสัมภาษณ์อาการโรคขาอยู่ไม่สุขในผู้ป่วยโรคพาร์กินสันด้วยแบบสอบถาม the Cambridge-Hopkins diagnostic questionnaire for RLS (CH-RLSq) ผู้ป่วยที่มีประวัติโรคไตวายเรื้อรังปลายประสาทเสื่อม โรคไขสันหลัง และมะเร็งจะถูกคัดออกผู้ป่วยได้รับการตรวจเลือดดูระดับเฟริติน*

ผลการศึกษา: *ผู้ป่วยโรคพาร์กินสันที่เข้าร่วมการวิจัยมีทั้งหมด 183 ราย มีผู้ป่วยเพียง 3 รายเท่านั้นที่ตรงตามหลักเกณฑ์การวินิจฉัยโรคขาอยู่ไม่สุข (1.6%) หนึ่งในผู้ป่วย 3 ราย มีระดับเฟริตินในเลือดเท่ากับ 31.9 mg/ml เมื่อคัดผู้ป่วยรายนี้ออก ความชุกโรคขาอยู่ไม่สุขในผู้ป่วยโรคพาร์กินสันจะลดเหลือ 0.98% จากการวิเคราะห์ปัจจัยต่าง ๆ ได้แก่ อายุ เพศ อายุ เมื่อเริ่มมีอาการโรคพาร์กินสัน ระยะเวลาที่เป็นโรคพาร์กินสัน ความรุนแรงของโรคพาร์กินสันไม่มีความแตกต่างกันทางสถิติระหว่างผู้ป่วยที่เป็นและไม่เป็นโรคขาอยู่ไม่สุข ผู้ป่วยที่ได้รับการผ่าตัดกระตุ้นสมองส่วนลึก (Deep Brain Stimulation) จำนวน 5 ราย ไม่มีอาการของโรคขาอยู่ไม่สุข*

สรุป: *ความชุกของโรคขาอยู่ไม่สุขในผู้ป่วยไทยที่เป็นโรคพาร์กินสัน ต่ำกว่าความชุกในประเทศอื่นมาก โดยเฉพาะในทวีปยุโรปและสหรัฐอเมริกา*