Sleep Medicine ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Restless legs syndrome, a predictor of subcortical stroke: a prospective study in 346 stroke patients

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ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 18 May 2015
Accepted 27 May 2015
Available online

Keywords:
Cerebrovascular disease
Stroke
Restless legs syndrome
Sleep

ABSTRACT

Objective: The objective of this study was to assess the prevalence of restless legs syndrome (RLS) among patients with stroke and to examine the anatomical correlation between location of stroke and RLS symptoms.
Methods: We administered a pre-structured sleep questionnaire to consecutive stroke patients seen in our neurology services department over a 3-year period. Unconscious (Glasgow Coma Scale score <15) or aphasic, renally impaired, or neuropathic patients were excluded. Diagnosis of RLS was established according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG), and polysomnography was conducted.
Results: Of 346 stroke patients, 35 (10.11%) fulfilled IRLSSG diagnostic criteria for RLS, which had existed for an average (±standard deviation) of 60 ± 40 months before stroke. The mean age of onset was 52.94 (±10.32) years. Twenty-four patients (68%) had RLS symptoms contralateral to the hemisphere involved in the stroke (eight with unilateral and 16 with grossly asymmetrical RLS). Twenty-nine of 35 patients (82.86%) had imaging evidence of subcortical (16 with hemorrhagic and 13 with ischemic) stroke. Patients with pre-stroke RLS differed from those without it only by subcortical location of the stroke (82.9% vs 31.5% respectively, $p < 0.001$). The most significant differentiating factor between patients with subcortical stroke and those with cortical stroke was pre-stroke RLS (22.83% vs 2.74%, $p < 0.001$), the others being history of hypertension and hemorrhagic stroke type.
Conclusion: RLS, especially unilateral or asymmetrical, might frequently pre-exist in patients presenting with subcortical stroke. The common laterality may suggest an important predictive value for RLS, and may form an important point for future research.

1. Introduction

Restless legs syndrome (RLS), first described by Ekbom in 17th century, is a common sleep-related movement disorder [1]. RLS is characterized by four essential criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) [2]: namely, an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; beginning or worsening during periods of rest or inactivity, such as lying down or sitting; partial or total relief by movement, such as walking or stretching, at least as long as the activities are continued; and worsening in the evening or at night as compared to the daytime, or occurring only in the evening or night. The prevalence of RLS is around 3%–4% in the general population and increases with age [3–5]. Nearly 80% of RLS patients also have periodic limb movements (PLMs) during sleep [6].

A number of modifiable as well as non-modifiable risk factors have been recognized for stroke occurrence; however, when taken individually, these do not predict stroke [7]. With the exception of transient ischemic attacks [8] and detection of stenosis of major vessels supplying the brain [9], there are no manifestations that have a predictive potential for future thrombo-embolic stroke occurrence. Arrhythmias such as atrial fibrillation, atrial flutter on electrocardiography, presence of thrombus, and wall defects on echocardiography also offer predictive potential for cardio-embolic stroke [10].

Few published studies have reported cases of RLS and PLMs associated with stroke [11–15], generally those involving the area of basal ganglia, corona radiata, or other subcortical areas [16]. There is also growing evidence that heart disease, hypertension, and stroke are linked with RLS/PLMs [17,18]. Walters et al. reported more cases of frequent clinical and silent stroke among patients with RLS compared to controls without RLS; although this difference was not statistically significant [19].

During our detailed evaluation of patients with stroke, for pre-existing sleep problems, as part of an ongoing trial, many patients and/or their caregivers reported history fulfilling IRLSSG criteria for RLS diagnosis. This study was therefore initiated to evaluate the

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http://dx.doi.org/10.1016/j.sleep.2015.05.025
1389-9457/

prevalence of RLS before the occurrence of stroke and to evaluate whether it might have predictive value for the occurrence of stroke.

2. Methods

This study was prospective in design and was conducted over a 3-year period, from 2010 to 2013, at our quaternary care referral hospital institution. The study protocol was approved by ethical committee of All India Institute of Medical Sciences (AIIMS), New Delhi.

2.1. Study subjects

Consecutive stroke patients who presented to a single unit of the neurology department at our center were enrolled. Patients who were clinically diagnosed with first-ever ischemic or hemorrhagic stroke (up to four weeks from ictus), were capable of giving detailed history, and who had computed tomography (CT)/magnetic resonance imaging (MRI) (brain) findings supporting clinical diagnosis of stroke were included in the study. Patients excluded were those with any other pre-existing neurological disorder, eg, neurodegenerative diseases or epilepsy, altered consciousness (Glasgow Coma Scale score <15), residual aphasia restricting communication, pre-existing chronic kidney disease, neuropathy, diagnosed iron deficiency anemia, or malignancy.

2.2. Clinical evaluation

2.2.1. Routine

Detailed clinical evaluation was carried out through a pre-structured sleep questionnaire encompassing detailed evaluation of RLS and other associated sleep disorders (if any).

Similarly, details about stroke location, arterial territory or region of hemorrhage, risk factors, and deficits were collected and tabulated for each patient by means of another pre-structured questionnaire.

2.2.2. Systematic questionnaire-based evaluation

The Berlin Questionnaire, Epworth Sleepiness Scale, and IRLSSG Rating Scale were administered to all patients. Diagnosis of RLS was made according to the National Institutes of Health IRLSSG diagnostic criteria only if there was agreement between independent blinded evaluation by two experienced sleep physicians (A.G. and G.S.).

2.2.3. Investigation-based evaluation

Nerve conduction studies, serum ferritin levels apart from those observed on routine hemogram and biochemical laboratory tests (liver function, kidney function, lipid profile, calcium studies, and thyroid functions), were performed for all patients diagnosed as RLS. Overnight polysomnography was also performed, when feasible, in patients who consented to this procedure.

2.3. Statistical analysis

STATA version 11.2 was used for statistical analysis. The Student t test was used to analyze continuous data with normal distribution, and the Wilcoxon rank-sum test was used for continuous data without normal distribution. The χ^2 test was used for categorical parameters.

3. Results

A total of 358 patients were eligible for enrollment during the study period; among these, 12 were excluded because of inadequate history. Of 346 patients (277 male and 69 female), 61 patients and their caregivers provided history of lower limb discomfort and pain; 35 (29 male and six female) fulfilled the diagnostic criteria for RLS, having begun at variable duration before the stroke ictus, and eight patients (seven male and one female) developed RLS symptoms following the occurrence of the stroke (Fig. 1A).

3.1. RLS characteristics

The prevalence of pre-stroke RLS was 10.11%, and the mean age at the time of diagnosing RLS was 54.87 years (±12.03 years). The mean duration of RLS before stroke was 51.5 months (±47.75 months), and the median duration of RLS among patients with subcortical stroke vs cortical stroke was 60 months (range, 10 days–240 months) vs 30 months (range, 3–60 months) ($p = 0.17$). Of 35 patients, eight had strictly unilateral RLS symptoms, 16 had asymmetrical involvement, and 11 had bilaterally symmetrical RLS symptoms. Among these, 24 (68.57%) patients had RLS symptoms contralateral to the hemisphere affected by stroke (Table 1).

The mean IRLSSG score was 14.42 (±5.4). Two patients had a positive family history of RLS and the mean Epworth Sleepiness Scale score was 6.09 (±1.68) (Table 2).

One patient (no. 26, Table 1) fulfilled criteria for RLS strictly confined to one lower limb for two years preceding stroke. Acute stroke in this patient comprised right hemiparesis. At the ictus, RLS symptoms became bilateral, still continuing to be much worse on the right side. MRI revealed subcortical infarcts on both sides. On the other hand, another patient (no. 28, Table 1) had a history of repetitive lower limb jerking every few minutes, more on the side of the hemiparesis, three months preceding the stroke ictus.

3.2. Investigations among stroke patients with history of RLS

Serum ferritin was low (<45 ng/mL) in one patient, and two patients had unrecordable sympathetic skin responses. Nerve conduction studies were normal in all patients.

Overnight polysomnography could be conducted in 16 patients, of whom 14 patients were found to have obstructive sleep apnea (OSA) (Apnea–Hypopnea Index [AHI] > 5), and six had periodic limb movements. The mean periodic limb movement index was 8.93 (± 6.8) (Table 2).

3.3. RLS treatment

Depending on the severity of symptoms, patients were offered symptomatic treatment with dopamine agonists. Eight patients received either low-dose pramipexole or ropinirole, whereas two patients received gabapentin (Table 1). All showed at least >50% improvement of symptoms in temporal relationship with initiation of treatment. Follow-up information was unavailable for two more patients.

3.4. Stroke characteristics among patients with pre-stroke RLS, and the stroke–RLS relationship

Among the 35 patients who had RLS preceding the stroke, 29 (82.8%) had subcortical strokes, with infarcts or hemorrhages located in the subcortical areas including the basal ganglia and thalami, 17 with stroke involving the basal ganglia, six with subcortical white matter (three internal capsules, one corona radiata, two centrum semiovale) infarcts, six with thalamic stroke, and six with cortical lesion and other posterior circulation stroke. Hence, a total of 22.83% (29 of 127) patients with subcortical strokes reported RLS, compared with 2.74% (six of 210) of those with cortical-based strokes (Fig. 1B).

Patients with pre-stroke RLS differed from those without it, only by subcortical location of the stroke (82.9% vs 31.5% respectively,

Please cite this article in press as: Anupama Gupta, Garima Shukla, Afsar Mohammed, Vinay Goyal, Madhuri Behari, Restless legs syndrome, a predictor of subcortical stroke: a prospective study in 346 stroke patients, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.05.025