RESTLESS LEG SYNDROME IN PATIENTS WITH MULTIPLE SCLEROSIS

Thesis

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LIST OF CONTENTS

LIST OF ABBREVIATIONS

BIPAP	Bi-Level Positive Air Way Pressure
CMT2	Charcott-Marie-Tooth neuropathy Type 2
CNS	Central Nervous System
CPG	Central Pattern Generator
CRD	Circadian Rhythm disorders
CSA	Central Sleep Apnea
CSF	Cerebrospinal fluid
D2RBP	Dopamine 2 receptor binding potential
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EMG	Electromyography
ESS	Epworth Sleepiness Scale
fMRI	Functional Magnetic Resonance Imaging
ICSD	International Classification of Sleep Disorders
IRLS	International Restless Legs Scale
IRLSSG	International Restless Leg Syndrome Study Group
LOD	Logarithm of the Odds
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSSS	Multiple Sclerosis Severity Scale

NCV	Nerve Conduction Velocity
NREM	Non Rapid Eye Movement
OSA	Obstructive Sleep Apnea
PD	Parkinson's Disease
PET	Positron Emission Tomography
PLMW	Periodic Leg Movement during Wakefulness
PLMS	Periodic Leg Movement during Sleep
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement
RLS	Restless Leg Syndrome
RP	Relapsing Progressive
RR	Relapsing Remittent
SAS	Self-rated Anxiety Scale
SCN	Suprachiasmatic nucleus
SDS	Self-rated Depression Scale
SIT	Suggested Immobilization Test
SOREMPs	Sleep Onset Rapid Eye Movement Periods
SN	Substantia Nigra
SPECT	Single Photon Emission Computed Tomography

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Restless legs syndrome (RLS) is a sleep-related movement disorder characterized by an urge to move the legs associated with an unpleasant sensation in the lower limbs, typically occurring when patients are at rest in the evening and at night. Symptoms are partially or totally relieved by movement. RLS can lead to the disturbance of sleep and impaired quality of life ***(Allen et al., 2003)***.

RLS is generally considered to be idiopathic (primary) or symptomatic (secondary). The primary form, (60–80% of all RLS) might better be defined as cryptogenic, indicating that in most cases the etiology and pathogenesis are uncertain, but leaving open the possibility of finding then exact origin and mechanisms. The secondary, or RLS associated conditions include end-stage renal disease, iron deficiency (with or without anemia), the neuropathies and radiculopathies, rheumatoid arthritis, the myelopathies, syringomyelia, Parkinson's disease (PD), and pregnancy. ***(Zucconi and Ferini -Strambi, 2004)***. The association of RLS and Multiple Sclerosis (MS) has been so consistent that it has recently been suggested that MS should be another recognized secondary cause for RLS ***(Deriu et al.,2009)***.

MS is a chronic central nervous system autoimmune demyelinating disease that most commonly affects people

between the ages of 20 and 50 years, with a worldwide prevalence of approximately 2.5 million people. The disease is characterized by relapsing and remitting neurological symptoms, such as weakness, numbness, vertigo, cognitive changes and blindness, leading long term to physical disability ***(Multiple Sclerosis Society America, 2009)***.

The clinical spectrum of MS has changed over the past few years due to new disease modifying therapies ***(Boissy and Fox, 2007).*** However, several symptoms may have serious implications for patient disability. Sleep disturbance, fatigue and depressive symptoms are frequently described in association with impaired quality of life ***(Kaynak et al., 2006)***.

Sleep disorders are pervasive in patients with MS, although clinically under recognized by most physicians. Approximately half of all patients with MS report sleep-related problems. Physical and psychological factors such as pain, depression, sleep-disordered breathing; disease severity and site of lesion all contribute to sleep disruption. The most common sleep disorders seen in patients with MS include insomnia, nocturnal movement disorders, sleep disordered breathing, narcolepsy, and rapid eye movement sleep behavior disorder. Disrupted sleep has the potential to cause daytime somnolence, increased fatigue, non refreshing sleep, worsening depression and lowered pain threshold. An increased clinical awareness of sleep-related problems is warranted in this patient's population because they are extremely common and have the

potential to negatively impact overall health and quality of life in patients with MS ***(Leo et al.,1991;Tachibana et al.,1994; Achiron et al.,1995; Felming wt al.,2005)***.

Fatigue is still one of the most common and disabling symptoms of MS patients affecting as many as 70% in some studies .Controversy remains over the causes of fatigue in MS and attempts have been made to correlate fatigue with clinical disability, disease progression and immunological markers ***(Alarcia et al., 2005)***.

RLS has been described to be common in MS ***(Manconi et al.,2007)***. However, the relationship between RLS and sleep quality, fatigue and clinical disability in MS patients has not been fully investigated ***(Moreira, 2008)***.

Although the etiopathogenesis of RLS is still unknown, several lines of evidence suggest a dopaminergic system dysfunction as the basic mechanism ***(Reynolds et al.,1986)***. The neuroanatomic basis of this dysfunction is also unclear, but a hyper excitability of the spinal locomotor generator, due to an impairment of inhibitory supraspinal descending neurons to the dorsal spinal gray matter, has been postulated ***(Clemens et al., 2006)***.

A possible causal relationship between MS and RLS has been reported. ***Kilfoyle et al., (2006)*** Given the fact that MS is sometimes a disease of precise neurological localization, attempts

to establish a connection between spinal cord lesion and RLS symptoms have been made without success ***(Gomez-Choco et al, 2007)***. More recently, cervical cord lesion has been associated with the presence of RLS suggesting that MS is actually a cause of secondary RLS ***(Manconi et al, 2008a)***.

In patients with MS, RLS symptoms may be the consequence of specific lesions of nervous-system structures or pathways involved in the etiology of RLS. Patients with MS with a higher global EDSS score and a more severe MS course, as compared with patients with a milder MS course, might have more opportunities to develop damage in specific neurologic regions involved in RLS pathogenesis. The dopaminergic hypothalamic-spinal connection descending from the A11 nucleus to the dorsal gray horns might be a possible lesion target in this mechanism. Several lines of evidence suggest that RLS symptoms may be induced by a dysfunction of this pathway that, in turn, would disinhibit lower spinal levels, triggering the typical RLS phenotype ***(Manconi et al., 2007)***.

Despite the fact that symptomatic treatment for RLS is available, it is still an under-recognized condition and frequently MS patients remain undiagnosed and untreated. RLS has a negative impact on sleep, quality of life and cognitive functions and higher awareness of RLS among physicians is warranted ***(Moreira, 2008)***.

AIM OF THE WORK

1. To study the existence of RLS in Multiple Sclerosis patients.
2. To correlate MRI findings to RLS.

RESTLESS LEG SYNDROME

Introduction

RLS is a distressing and potentially disabling sleep disorder that is characterized by a compelling urge to move the legs that is usually accompanied by unpleasant sensations in the lower extremities, begins or worsens during periods of rest, worsens during the evening and night time hours, and is partially or totally relieved by movement. The diagnosis is based on the patient's clinical description and the presence of typical symptoms in diagnostic criteria. The diagnosis is further supported by the presence of periodic limb movements in sleep (PLMS) and positive response to dopaminergic treatment ***(Allen et al.,2003; Hening et al., 2004)***.

RLS is associated with profound reductions in quality of life, comparable to or worse than those documented in diabetes, PD, stroke, and other serious chronic conditions. RLS has also been linked to significant impairment in sleep, mood, and physical health, and has been associated with substantial economic and social burden. RLS is a common cause of insomnia ***(Innes et al., 2012)***.

RLS remains one of the most intriguing and commonest chronic sensorimotor disorders, yet it is still a poorly recognized

condition in primary care settings as physicians are frequently unaware of the condition and misdiagnosis is common. Even though RLS was first identified and characterized in the forties, it was only in 2003 that the International Restless Legs Syndrome Study Group (IRLSSG) outlined its clinical features ***(Allen et al., 2003; Allen et al., 2005).***

The underlying neurophysiological and biochemical mechanisms are currently being investigated and recent animal and molecular studies have also begun to elucidate the still uncertain nature of the basic pathophysiology of RLS. RLS appears increasingly to be a complex disorder whose underlying pathophysiology is still unraveled. However, this should not impede clinical and fundamental research efforts for better recognition of the disease ***(Barriere et al., 2005)***.

Epidemiology

Prevalence rates of RLS, at least in Western countries, clearly identify this disorder as one of the most common neurological movement disorders. However, prevalence estimates in general populations do not overlap across studies even when the IRLSSG criteria are strictly applied. The subjective nature of the complaints, the fluctuating and intermittent course of initial symptoms, different targeted patient populations and the various methodological tools may partly account for these discrepancies. If only IRLSSG criteria-based studies in Western countries are

considered, the RLS prevalence rate ranges from 7.2 to 11.5% in the general population ***(Allen et al., 2005; Bjorvatn et al., 2005).***

Prevalence seems to increase with age, although onset before 20 years of age is not uncommonly reported in clinical studies and may decrease with age in elderly men and remain stable in elderly women. There is a female preponderance ranging from 13-17% ***(Lavigne and Montplaisir, 1994)*** to 13.8% ***(Rothdach et al, 2000)***, although in Japan it seems to be greater among men (especially those aged 40–49 years) than women ***(Kageyama et al., 2000)***. ***Phillips et al., (2000)*** by means of a questionnaire, found an age adjusted prevalence of RLS in adults (1803 subjects) of 10% with a male to female ratio of 1:1, and a figure increasing with age: 3% in those between 18 and 29 years, 10% between 30 and 79 years, and 19% over 80 years. They found the significant associated factors to be diminished general health. The influence of variable genetic susceptibility or environmental factors may determine regional variations (for example, in Caucasian vs. Asian vs. African). Finally, different methodological tools (questionnaires, telephone interviews, direct observations) and different diagnostic criteria (ICSD 1990 vs. IRLSSG 1995) may explain some of these differences ***(Zucconi and Ferini-Strambi, 2004)***.

No definite age of onset can be determined from available studies. Onset before 18 years of age has been reported ***(Ekbom, 1960; Ohayon and Roth, 2002)*** and 38–45% of adults with RLS