Comparison of prevalence rates of Restless Legs Syndrome, self-assessed risks of Obstructive Sleep Apnea, and daytime sleepiness among patients with Multiple Sclerosis (MS), Clinically Isolated Syndrome (CIS) and Neuromyelitis Optica Spectrum Disorder (NMOSD)

Vahid Shaygannejad[1,2*], Dena Sadeghi Bahmani[1,3,4,5], Parisa Soleimani[1], Omid Mirmosayyeb[1,6], Mehran Barzegar[1], Babak Amra[7], Serge Brand[3,4,5,8]

1 Isfahan Neurosciences Research Center, Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

2 Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

3 University of Basel, Psychiatric Clinics (UPK), Center of Affective, Stress and Sleep Disorders (ZASS), Basel, Switzerland

4 Kermanshah University of Medical Sciences (KUMS), Substance Abuse Prevention Research Center, Health Institute, Kermanshah, Iran

5 Kermanshah University of Medical Sciences (KUMS), Sleep Disorders Research Center, Kermanshah, Iran

6 Medical Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran

7 Pulmonary Unit, Department of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

8 University of Basel, Department of Sport, Exercise, and Health, Division of Sport Science and Psychosocial Health, Basel, Switzerland

*Corresponding author:

Vahid Shaygannejad, MD
Isfahan Neurosciences Research Center
Alzahra Research Institute
Isfahan University of Medical Sciences
Isfahan, Iran
shaygannejad@med.mui.ac.ir

Abstract

Background: Prevalence rates for Restless Legs Syndrome (RLS) and risk of Obstructive Sleep Apnea (OSA) in individuals with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Clinically Isolated Syndrome (CIS) are unknown. The aims of the present study were to assess symptoms of RLS and self-assessed risks of OSA in individuals with NMOSD and CIS, to compare these prevalence rates with those of persons with multiple sclerosis (MS), and to associate RLS and OSA with EDSS scores and daytime sleepiness, fatigue, paresthesia, and medication.

Methods: A total of 495 individuals (mean age = 34.92 years, 84.9% females) were assessed. Of these, 24 had NMOSD, 112 had CIS and 359 had MS. Trained neurologists ascertained individuals' neurological diagnoses, assessed their EDSS scores, and conducted a clinical interview to assess RLS. Additionally, participants completed questionnaires covering sociodemographic information, risks of snoring and obstructive sleep apnea, daytime sleepiness, fatigue, paresthesia and medication.

Results: Prevalence rates of RLS were 45.8% in NMOSD, 41.1% in CIS, and 28.7% in MS. Prevalence rates of self-assessed risks of OSA were 8.3% in NMOSD, 7.7% in CIS, and 7.8% in MS; these rates were not significantly different. Across the entire sample and within the diagnostic groups, RLS and OSA scores were unrelated to EDSS, daytime sleepiness, fatigue or medication.

Conclusions: Individuals with NMOSD, CIS and MS have high prevalence rates for RLS and self-assessed risks of OSAs, which are unrelated to EDSS, daytime sleepiness, fatigue, paresthesia, or medication. Sleep issues should be monitored during routine check-ups for individuals with NMOSD and CIS.

Key-words: Multiple Sclerosis; Clinically Isolated Syndrome; Neuromyelitis Optica Spectrum Disorder; daytime sleepiness; Restless Legs Syndrome; Obstructive Sleep Apnea;

1. Introduction

Research indicates that mental and somatic issues are associated with impaired sleep. As regards neurological diseases, sleep disturbance is one of the first responses to chronic inflammatory diseases [1-3], and reduced sleep quality together with daytime sleepiness are associated with adverse consequences for quality of life[1].

In the present study, we focused on the prevalence rates for Restless Legs Syndrome (RLS) and self-assessed risks of Obstructive Sleep Apnea (OSA) in individuals with Neuromyelitis Optica Spectrum Disorder (NMOSD) and Clinically Isolated Syndrome (CIS), as compared to persons suffering from multiple sclerosis (MS). While MS sufferers report higher rates of RLS and OSAs than healthy controls [4-15], we do not have the equivalent prevalence rates for individuals with NMOSD or CIS.

Restless Legs Syndrome is a clinically diagnosed neurological disorder. Symptoms are unpleasant sensations in the legs, the worsening of these sensations during rest, relief when moving, and exacerbation of the sensations in the evening [16] The prevalence rate of RLS in the general population is about 4.2% [16]. For MS sufferers, prevalence rates appear to vary according to the type of MS. Whereas some studies [17] have reported higher RLS prevalence rates among individuals with primary progressive MS, and lower RLS prevalence rates among individuals with relapsing-remitting MS (RRMS), Douay et al. [18] reported higher RLS prevalence rates among individuals with relapsing-remitting MS. Vavrova et al. [19], however, reported higher RLS prevalence rates among individuals with secondary progressive MS (SPMS). We therefore assessed the MS prevalence rates separately for RRMS and SPMS.

Obstructive Sleep Apnea (OSA) is a sleep disorder resulting from the reduction or complete cessation of breathing [20-22]. In most cases OSA is peripherical; that is to say the upper airways are mechanically obstructed, resulting in a decrease in O_2-saturation which in

turn produces an O_2-CO_2-inbalance and consequently re-arousal of the resting organism. While Braley et al. [21, 23] estimated that up to 21% of individuals with MS suffer from OSAs, to our knowledge the corresponding rates for individuals with either CIS or NMOSD are not known. OSAs are associated with a broad range of cardio-vascular and health-related diseases [24]. Knowledge of the prevalence rates for OSA among individuals with NMOSD, CIS, and MS might therefore help to prevent other health-related problems. Accordingly, in the present study participants self-assessed the risks of obstructive sleep apnea.

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a chronic inflammatory disease characterized by the involvement of the optic nerve, the spinal cord and the brain [25]. Formerly, NMOSD was considered a variant of Multiple Sclerosis. [26]. However, although NMOSD and MS have similar clinical features, they have different pathological and immunological pathways [27]. The antibody against aquaporin4 (anti-AQP4) in the central nervous system plays an important role in the pathogenesis of NMOSD, and this feature allows us clinically to distinguish NMOSD from MS [27, 28]. Moreover, the majority of individuals with NMOSD experience both a relapsing course of illness and severe symptoms, either of which may lead to severe disability, along with a reduced health-related quality of life (HRQOL). Barzegar et al. (2018, 2019) were able to showed that, compared to individuals with MS, individuals with NMOSD had lower scores for health-related quality of life, along with higher scores for depression and sleep disturbances. However, to our knowledge the prevalence rates for RLS and OSAs in individuals with NMOSD, have yet to be determined.

Clinically Isolated Syndrome (CIS) has been described by Armoiry et al. [29] as isolated events of symptomatic neurological disturbance which last more than 24 hours and which are considered the first signs of clinical demyelination of the central nervous system. Additionally, the brief description provided by Armoiry et al. [29] indicates that the clinical

syndromes are usually mono-focal but sometimes also multi-focal. Armoiry et al. [29] also stressed that people with CIS are at increased risk of developing MS, but without being formally diagnosed with MS [30]. Langer-Gould et al. [31] also noted that there were no reliable prevalence rates for CIS but that in a large sample of individuals with neurological diseases the incidence of CIS varied between 2.4% and 6.8% depending on ethnicity and gender.

As regards sleep in individuals with CIS, to our knowledge only one study has assessed prevalence rates in this group. Gonzales-Platas et al.[32] conducted an observational study in the territory of Northern Tenerife and assessed 240 individuals with demyelinating disease, including 163 individuals with MS, 36 with clinically isolated syndrome (CIS), 26 with radiological isolated syndrome (RIS), and 15 with other demyelinating diseases (DD). Individuals completed a series of self-rating questionnaires covering subjective sleep, daytime sleepiness, Restless Leg Syndrome, Obstructive Sleep Apnea, fatigue, and quality of life. Results showed that compared to those with CIS, RIS and DD, individuals with MS reported more issues of insomnia, while for all other dimensions (RLS, OSAs, daytime sleepiness), no significant differences were observed between the groups. In brief, as regards sleep in individuals with CIS, only one study has examined this and shown that the prevalence rates of RLS and OSAs were comparable to prevalence rates for individuals with MS.

Next, there is some evidence that the occurrence of RLS can be associated with higher EDSS scores [17, 19, 33-35]. In the current study we therefore examined whether higher RLS scores were associated with higher EDSS scores.

Last, there are conflicting findings as regards the association between RLS and daytime sleepiness. While some studies have reported an association between higher RLS

scores and daytime sleepiness [17] others have not [33, 36, 37]. The present study has the potential to resolve this uncertainty one way or the other.

The following three exploratory research questions were formulated. First, we asked about the prevalence rates for RLS and self-assessed risks of OSA in individuals with NMOSD and CIS, as compared to MS sufferers. Second, we explored the associations between RLS, self-assessed risks of OSAs, and EDSS scores, daytime sleepiness, fatigue and paresthesia, both across the sample as a whole and within the subsamples of diseases. Third, we asked about participants' medication and its possible association with prevalence rates of RLS, and self-assessed risks of OSAs.

2. Method

2.1. Procedure

Individuals diagnosed with NMOSD, CIS or MS (RRMS; SPMS) were approached at the Isfahan University of Medical Sciences, Isfahan Neurosciences Research Center, Alzahra Research Institute, Isfahan (Iran), and asked to participate at the present study on sleep in individuals with neurological and neurodegenerative diseases. Eligible individuals were fully informed about the aims of the study and the anonymous data handling. Afterwards, individuals signed a written informed consent. Trained neurologists assessed EDSS scores, clinical psychologists performed a thorough clinical, psychiatric and sleep-related interview, and the individuals themselves completed a booklet of questionnaires covering sociodemographic and sleep-related matters. The ethical committee of the Isfahan University of Medical Sciences (IUMS; Isfahan, Iran) approved the study, which was performed in accordance with the rules laid down in the Declaration of Helsinki and its later amendments.

2.2. Samples

A total of 506 individuals with NMOSD, CIS or MS (RRMS; SPMS) were approached. Of these, 495 completed the study; eleven withdrew from participation or felt unable to comply with the study conditions. Inclusion criteria were: 1) age between 18 and 75 years; 2) diagnose of NMOSD, CIS or MS, as ascertained by a trained neurologist; 3) willing and able to comply with the study conditions (following the clinical interview; completing self-rating questionnaires); 4) signed written informed consent. Exclusion criteria were: 1) current comorbid psychiatric disorder such as substance use disorder, mood disorders (current manic or depressive episode); 2) acute suicidality; 3) currently unable to answer to a clinical interview and to complete self-rating questionnaires.

2.3. Tools

2.3.1. Expanded Disability Status Scale (EDSS)

Trained neurologists assessed individuals' degree of disability with the EDSS [38] The EDSS is an accepted and widely used tool for objective assessment of the disability levels of individuals with MS, CIS or NMOSD. The total score is on a scale from 0 to 10, with increments of 0.5–1.0, and with higher scores reflecting higher levels of disability. EDSS steps 1.0–4.5 refer to people with MS who are fully ambulatory. EDSS steps 5.0–9.5 are defined by impairment to ambulation. Meyer-Moock et al. [39] reported in their systematic review the high validity and reliability of the EDSS. Meyer-Moock et al. [39] also concluded that the EDSS is suitable for describing clinical status and degree of physical disability, and for monitoring disease progression.

2.3.2. Restless Legs Syndrome

To diagnose Restless Legs Syndrome, experienced neurologist employed the Restless Legs Syndrome – Diagnostic Index (RLS-DI [40]). The following five mandatory questions

must be answered with “yes, sometimes experienced in one to four days of a week” (= one point), or with “yes, regularly experienced in more than five days of a week” (= two points).

Question one: “Feel the urge to move legs (and arms)?”

Question two: “When feeling the urge to move legs (arms), then paresthesia of tension, pain, tingling, stinging?”

Question three: “Do urge to move legs (arms) and feeling of paresthesia begin or worsen when being at rest (sitting; lying) or when not moving at all?”

Question four: “Urge to move or paresthesia do partially or fully disappear when moving (walking; stretching)?”

Question five: “Urge to move or paresthesia are more prominent in the evening and night, when compared to daytime?”

Restless Legs Syndrome was objectively diagnosed, when the sum score was 5 points or higher.

Besides the RLS-DI, also the International Restless Legs Study Group (IRLSSG) rating scale [16] was employed in a face-to-face interview following the procedure as set out by the International RLS Study group [41]. Questions focus on RLS-related severity such as RLS discomfort in legs and arms, need to move around for relief from RLS symptoms, and frequency of RLS symptoms. Answers are given on 5-point Likert scales ranging from 0 (none) to 4 (very severe), with higher scores therefore reflecting more marked symptoms of RLS (Cronbach’s $\alpha = 0.91$). In addition, a categorical variable (no RLS or mild RLS: 0-10 points; moderate RLS: 11-20 points; severe RLS: 21-30 points; very severe RLS: 31-40 points) was derived.

2.3.4. Self-assessed risks of Snoring and sleep apnea; Obstructive Sleep Apnea

To self-assess risks of snoring and sleep apnea, two self-rating tools were employed, the STOP-Bang [42] and the Berlin questionnaire [43].

2.3.4.1. STOP-Bang Questionnaire

The STOP-Bang questionnaire [42] is a self-report, forced-choice (yes/no) scale to rate the risks of suffering from obstructive sleep apnea. The questionnaire consists of four questions related to snoring (S), tiredness during the daytime (T), observed apneas (O) and high blood pressure (P; STOP). When two or more questions are answered with yes then the person has a higher risk for obstructive sleep apnea/hypopnea syndrome. The "Bang" portion is evaluated by assessing BMI >35 kg/m^2 (B), age (>50 years) (A), neck circumference (>40 cm) (N), and gender (male) (G). One point is assigned for each positive answer and zero for each negative answer. High risk for the Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) on the STOP-Bang is indicated when three or more of the eight questions are answered yes. The total score was treated as both a continuous variable a dichotomous variable (low risk vs. high risk). The STOP-Bang is a sensitive, reliable screening tool for OSA, frequently used in outpatient sleep clinics.

2.3.4.2. Berlin Questionnaire

Similar to the STOP-Bang, the Berlin Questionnaire (BQ) [43] is a questionnaire designed to self-assess the risks of suffering from Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS). The items are as follows: Category 1: 1. "Do you snore?" (yes/no/I don't know); 2. "Your snoring is…" (as loud as normal breathing/as loud as talking/louder than talking); 3. "How often do you snore?" (almost every day/3-4 times the week/1-2 times the week/1-2 times the months/rarely or never). 4. Has your snoring ever bothered other people?" (yes/no/I don't know); 5. Has anyone noticed that you stop breathing during sleep?"

(almost every day/3-4 times the week/1-2 times the week/1-2 times the months/rarely or never). Category 2: 6. “How often do you feel tired or fatigued after your sleep?” (almost every day/3-4 times the week/1-2 times the week/1-2 times the months/rarely or never). 7. “During your waking time, do you feel tired, fatigued or not up to par?” (almost every day/3-4 times the week/1-2 times the week/1-2 times the months/rarely or never). 8. “Have you ever nodded off or fallen asleep while driving a vehicle?” (yes/no). If your answer is ‘yes’; 9. How often does it occur? (almost every day/3-4 times the week/1-2 times the week/1-2 times the months/rarely or never). Category 3: 10. “Do you have high blood pressure?” (yes/no/I don’t know). High risk for Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) is defined when there are persistent symptoms (more than three or four times per week) in categories 1 and 2, and hypertension (P140/90 mmHg or use of medication) or BMI P30 kg/m^2 in category 3. Categories 1 and 2 are positive when the sum of all items is ≥ 2. Individuals are classified as having high risk for OSAHS if scores are positive in two or more categories. Individuals scoring positive in only one or none of the categories are classified as low risk. The sum score was treated as a continuous variable, while a dichotomous variable (low risk vs. high risk) was also calculated.

2.3.5. Daytime sleepiness (Epworth Sleepiness Scale; ESS)

The Epworth Sleepiness Scale [44] was employed to assess daytime sleepiness. This self-rating questionnaire consists of ten items rating the odds of dozing off in different activities. Answers are given on 4-point rating scales (0-3), with higher sum scores reflecting higher daytime sleepiness. The score can range from 0 to 30 points; a global score greater than 10 indicates excessive daytime sleepiness. ESS scores were treated as continuous and as dichotomous. The validity and reliability of the Farsi version have been established [45].

2.3.6. Fatigue

Participants completed the Fatigue Severity Scale (FSS; [46]) The FSS consists of nine items, and answers are given on 7-point rating scales ranging from 1 (not at all) to 7 (definitively/almost always), with higher scores reflecting higher levels of fatigue.

2.3.7. Paresthesia

Patients rated their degree of paresthesia on a 10-point visual analogue scale ranging from 0 (no sensations at all) to 10 (severe sensations) [47].

2.3.8. Medication

Participants were asked to bring their packages of NMOSD-, CIS-, or MS-related medications to the interviews so that the types of medication they were taking could be thoroughly assessed. Medical records provided an additional source of information about medications prescribed.

Medications were clustered into five groups: 1. Interferons such as Avonex or Rebif; 2.Glatiramer Acetate: Glatinamers; 3. Fumarates and immune suppressives 4. Monoclonal antibodies such natalizumab, rituximab; 5; others/unknown/missing.

2.3.9. Body Mass Index (BMI)

Individuals' height and weight were measured during the assessment.

2.4. Statistical analysis

A series of ANOVAs examined mean differences between individuals with NMOSD, CIS, and MS (RRMS; SPMS) with respect to age, EDSS scores, RLS scores, daytime sleepiness (ESS) scores, OSAs (StopBang; Berlin), fatigue, and BMI. Post-hoc analyses were

performed with Bonferroni-Holm corrections for p-values. With a series of X^2-tests, differences in prevalence rates for dichotomous dimensions of RLS scores, OSA scores and daytime sleepiness (ESS) were calculated between individuals with MS (RRMS; SPMS), CIS and NMOSD.

Pearson's correlations were computed between age, EDSS score, RLS scores, OSA scores, fatigue, and daytime sleepiness (ESS), both for the sample as a whole and separately for individuals with MS, CIS and NMOSD. Correlations of $r < .29$ were considered as small, $r = .30$ to .49 were considered as medium, and $r \geq .50$ were considered as large.[48]

Distributions of types of medication within and between the four groups of individuals (NMOSD; CIS; MS: RRMS; SPMS) were calculated using a X^2-test.

With a series of one-way ANOVAs it was determined whether age, EDSS, RLS, OSAs, daytime sleepiness, fatigue or paresthesia differed significantly between types of medication.

Finally, two-way ANOVAs were computed with the factors Medication (interferons; Glatiramer acetate; fumarates and immune suppressive; monoclonal antibodies) and Disease (NMOSD; CIS; MS: RRMS; SPMS) and the dependent variables age, EDSS, RLS, OSAs, daytime sleepiness, fatigue and paresthesia.

The nominal level of significance was set at alpha < .05. All statistical computations were performed with SPSS® 25 (IBM Corporation, Armonk NY, USA) for Apple® Mac®.

3. Results

3.1. Sample characteristics

A total of 495 individuals completed the study. Of these, 420 (84.9%) were female, and 75 (15.1%) were male. A total of 24 (4.8%) had NMOSD, 112 (22.5%) had CIS, and 359 (72,6%) had MS (RRMS: 309 (62,2%); SPMS: 50 (10.1%)). Gender ratio did not differ

significantly between the three groups: NMOSD (f: 22; m: 2); CIS (f: 99; m: 13); MS (f: 299; m: 60): $X^2(N = 495, df = 2) = 2.57, p = .28$.

3.2. Age, EDSS scores, Restless Legs Syndrome scores, self-assessed risks of Obstructive Sleep Apnea scores, daytime sleepiness (ESS), fatigue and paresthesia between individuals with NMOSD, CIS and MS.

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Table 1 about here

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Table 1 reports the descriptive and inferential statistical indices for age, EDSS scores, daytime sleepiness (ESS), fatigue, paresthesia, self-assessed risks of Obstructive Sleep Apnea scores (StopBang; Berlin), separately for individuals with NMOSD, CIS, and MS (RRMS; SPMS). Statistical indices are fully reported in the Tables and are not repeated in the text.

Age differed significantly between individuals with MS, CIS and NMOSD. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed individuals with MS were older than those with either CIS or NMOSD. Descriptively, individuals with CIS were older than those with NMOSD.

EDSS scores differed significantly between individuals with MS, CIS and NMOSD. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed higher EDSS scores in individuals with SPMS than those with RRMS, CIS or NMOSD. Descriptively, individuals with NMOSD had higher EDSS scores than those with CIS.

Restless Legs Syndrome scores differed significantly between individuals with MS, CIS and NMOSD. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed

higher RLS scores in individuals with SPMS and RRMS than those with CIS. There were no differences between individuals with CIS and NMOSD.

Self-assessed risks of Obstructive Sleep Apnea scores (StopBang; Berliner) differed significantly between individuals with MS, CIS and NMOSD. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed higher OSA scores in individuals with SPMS than those with either CIS or RRMS. There were no differences between individuals with either CIS or NMOSD.

As regards daytime sleepiness (ESS), no significant or descriptive mean differences were observed between individuals with MS, CIS, and NMOSD.

For fatigue, individuals with NMOSD had significantly lower scores than those with SPMS.

Paresthesia scores did not differ across the four groups.

3.3. Categories of RLS, self-assessed risks of OSA (StopBang; Berlin) and daytime sleepiness, separately for individuals with NMOSD, CIS and MS.

RLS scores, self-assessed risks of OSA scores and daytime sleepiness (ESS) scores were split into categorical variables. Table 2 reports the frequency, distribution and statistical calculations for these categorical variables between individuals with NMOSD, CIS and MS.

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Table 2 about here

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Individuals with CIS had lower moderate RLS scores that expected. Individuals with SPMS had higher moderate RLS scores that expected. Individuals with RRMS had more severe RLS scores that expected.

As regards OSAs, depending on the tool used for assessment, significant differences in the prevalence rates of OSAs either were (Stop-Bang) or were not observed (Berlin) between individuals with MS, CIS and NMOSD

As regards daytime sleepiness (ESS), no significant differences in the prevalence rates of daytime sleepiness were observed between individuals with MS, CIS and NMOSD.

To summarize, compared to individuals with CIS and NMOSD, occurrence of RLS was significantly higher in individuals with MS (SPMS), while no differences were observed between the three categories as regards OSAs (depending on the assessment tool) or daytime sleepiness.

3.4. Correlations between age, EDSS, RLS, daytime sleepiness (ESS), fatigue, paresthesia, and self-assessed risks of Obstructive Sleep Apnea (Stop-Bang; Berlin)

Table 3 summarizes the correlations between age, EDSS, RLS, dimensions of self-assessed risks of Obstructive Sleep Apnea (Stop-Bang; Berlin), daytime sleepiness (ESS), fatigue, and paresthesia for the entire sample (N = 495).

Greater age was significantly associated with higher EDSS, RLS, daytime sleepiness and self-assessed risks of Obstructive Sleep Apnea, though the correlation coefficients were small. Age was not associated with fatigue or paresthesia.

A higher EDSS score was associated with higher RLS, and self-assessed risks of Obstructive Sleep Apnea, though again correlation coefficients were small. EDSS was not associated with daytime sleepiness, fatigue or paresthesia.

Higher RLS scores were associated with higher fatigue, and self-assessed risks of Obstructive Sleep Apnea scores, but correlation coefficients were small.

Higher daytime sleepiness was associated with higher self-assessed risks of Obstructive Sleep Apnea scores, but the correlation coefficient was small.

A higher Fatigue score was associated with higher paresthesia scores.

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Table 3 about here

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When correlational computations were performed separately for individuals with NMOSD, CIS and MS, the pattern of results remained basically similar (Table 4).

NMOSD: Higher age was associated with higher EDSS, RLS, OSA and daytime sleepiness cores. A higher EDSS score was associated with higher RLS and OSA scores. Higher RLS scores were associated with higher fatigue and OSA scores. Daytime sleepiness was associated with RLS and OSA scores. Fatigue and paresthesia were associated. All correlation coefficients were small.

CIS: Higher age was associated with higher OSA scores. Higher EDSS scores were associated with higher RLS scores. A higher daytime sleepiness was associated with higher OSA scores. Fatigue and paresthesia were associated. All correlation coefficients were small.

MS: RRMS: Higher age was associated with higher EDSS scores, daytime sleepiness, and higher OSA scores (Stop-Bang). A higher EDSS score was associated with higher RLS scores. Higher RLS scores were associated with higher paresthesia and OSA scores. Daytime sleepiness was related to lower paresthesia scores, but unrelated to the EDSS, RLS and OSA

scores. Higher fatigue scores were related to higher OSAs (Berlin) and paresthesia scores. All correlation coefficients were small.

MS: SPMS: Higher age was associated with higher RLS and OSA scores. Higher RLS scores were associated with higher fatigue, paresthesia and OSAs. Fatigue and paresthesia were associated.

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Table 4 about here

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3.5. Medication

Table 5 reports the groups of medications for individuals with NMOSD, CIS and MS. Types of medications (interferons; glatiramer acetate; fumarates and immune suppressiva; monoclonal antibodies) and amount of medication did not significantly differ between individuals with NMOSD, CIS and MS (X^2(N = 495, df = 12) = 12.88, p = .38).

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Table 5 about here

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A series of one-way ANOVAs with Medication as independent factor and age, EDSS, RLS; OSAs, daytime sleepiness, fatigue, and paresthesia, confirmed that none of the dependent variables differed significantly between types of medication (all F's < 1.7, p's > .14). In addition, a series of two-way ANOVAs with the factors Medication and Disease, and with

age, EDSS, RLS; OSAs, daytime sleepiness, fatigue, and paresthesia as dependent variables showed no differences (all F's < 1.4, p's > .20).

4. Discussion

The key findings of the present study were that in a large sample of individuals diagnosed with either Neuromyelitis Optica Spectrum Disorder (NMOSD), Clinically Isolated Syndrome (CIS), or Multiple Sclerosis (MS), prevalence rates for Restless Legs Syndrome (RLS) and self-rated risks of Obstructive Sleep Apnea (OSA) were high. More specifically, individuals with MS (and particularly those with SPMS) had lower prevalence rates for RLS than individuals with CIS or NMOSD. However, prevalence rates for self-rated risks of OSA did not differ between individuals with NMOSD, CIS and MS, nor were such prevalence rates associated with EDSS or daytime sleepiness scores. Medication type was unrelated either to the nature of the illness or to the dimensions of age, EDSS, RLS, OSAs, daytime sleepiness, fatigue, and paresthesia. The present study adds to the current literature in an important way as to our knowledge this is the first study to report and to compare prevalence rates for sleep-related issues of individuals with NMOSD, CIS or MS, and to relate these rates to medication and to other psychological dimensions.

Three research questions were formulated, and each of these is considered in turn.

Our first research question concerned the prevalence rates of RLS and self-rated risks of OSA in individuals with NMOSD and CIS, compared to those with MS. We found that individuals with secondary progressive MS had the lowest prevalence rates for RLS, higher than those with NMOSD, CIS or RRMS.

Prevalence rates for RLS between individuals with NMOSD and CIS did not differ.

As regards self-assessed risks of OSAs, again, prevalence rates between individuals with NMOSD and CIS did not differ, while those with MS had higher prevalence rates (Table

2). Table 2 also shows that prevalence rates of self-assessed risks of OSAs differed as a function of the assessment tool; it follows that assessing OSAs subjectively via self-rating tools carries a risk of imprecision. This points to the desirability of assessing OSAs, including snoring, using objective tools [24].

Our second research question concerned the associations between RLS, OSAs, and EDSS scores, daytime sleepiness, fatigue and paresthesia, both across the sample as a whole and within the subsamples of diseases (Tables 3 and 4). It turned out that higher EDSS scores were associated with higher RLS and self-assessed risks of OSA scores; this pattern was particularly pronounced in individuals with NMOSD (Table 4). As a general observation, the present patterns of results are consistent with previous findings for MS sufferers [17, 19, 33, 35]. However, the present results expand upon previous work in demonstrating this association in individuals with NMOSD and CIS.

We also found significant correlations between symptoms of RLS, fatigue and paresthesia (entire sample and in MS sufferers). This points to a difficulty in separating the symptoms of RLS, fatigue and paresthesia, suggesting they may have a common basis in tactile misperception.

Our third research question addressed participants' medication and its possible association with prevalence rates for RLS, and self-assessed risks of OSA. We found disease-related medications to be unrelated to either RLS or self-assessed risks of OSA. Furthermore, as shown in Table 5, types of medications were not related to the nature of the illness, and statistical indices show that type of medication was not related in any systematic way to scores for RLS, OSAs, EDSS, daytime sleepiness, age, fatigue, or paresthesia. This pattern of results needs to be replicated and should for the present be treated with caution, in particular due to the high frequency of "missings", though we believe that the influence of MS-, CIS-

and NMOSD-related medication should not be overestimated when investigating sleep, daytime sleepiness, fatigue and paresthesia in individuals with these disorders.

The evidence provided by this study does not allow a deeper understanding as to why prevalence rates of RLS and self-assessed risks of OSAs were higher in all groups of disease than in the general population. That is to say, we can offer no conclusions as to the neurophysiological mechanisms underlying the higher prevalence rates of RLS and OSA that we observed.

As regards RLS, Sieminski et al. [49] appear to present the most comprehensive neuronal account of the high overlap between RLS and MS. Briefly, inflammatory processes as observed in individuals with MS may lead to an up-regulation of cytokines (Il-6, TNF-α) and nitric oxide. Increased cytokines lead to an intra-cellular retention of iron, which in turn is the cause of the destruction of the cell and of iron deficiency in other areas of the brain. The unbalanced stores of iron leads to a downregulation of dopamine and of myelination. A decrease in myelination appears to be causally linked to the development of RLS. At the same time, the upregulation of nitric oxide suppresses the expression of myelin proteins, which ultimately results in demyelination and symptoms of both RLS and MS.

As regards a neurological explanation for the high prevalence rate of OSA in individuals with MS, first of all Kaminska [50] proposed that Obstructive Sleep Apnea might negatively impact on symptoms of MS via increased fatigue. Roelcke et al. [51] showed a reduction in cerebral glucose metabolism, and Inglese et al. [52] observed a hypoperfusion of specific gray matter regions, always in individuals with MS. Importantly, OSA also causes gray matter abnormalities and these could be exacerbated in typical MS-related changes. Next, [53] showed that OSA and systemic inflammations increase, leading to the possibility that OSA might cause systemic inflammations, which are also typical in individuals with MS. Last, Ferini-Strambi et al. [54] and Auer et al. [55] proposed that, in MS, demyelinating

lesions may occur in the brain stem, and particularly in the reticulospinal pathways which regulate motor control of the upper regulatory tract and which may be impaired leading to not peripheral but to central OSA.

To the best of our knowledge, no theoretical or neurophysiological account has yet been offered for the occurrence of RLS and OSA among individuals with CIS and NMOSD. However, given their pathophysiological similarities to MS, we suggest that mechanisms similar to those described above for individuals with MS might also be applicable for individuals with CIS and NMOSD.

Despite the novelty of the findings, several limitations warn against overgeneralization of the present findings. First, it would have been helpful to know the impact of RLS and self-assessed risks of OSAs on individuals' subjective sleep quality. Future studies might therefore include, for example, the Pittsburgh Sleep Quality Index [56] or the Insomnia Severity Index [57] to assess individuals' subjective feelings of sleep quality and restoring sleep. Second numerous studies have shown that restoring sleep is associated with regular physical activity. In this respect, Sadeghi Bahmani et al. (2019a,b) have reported positive effects of regular physical activity on objective and subjective sleep patterns in female patients with MS. To our knowledge there is no equivalent evidence for individuals with CIS and NMOSD. Third, RLS [58] and OSAs [59] are associated with higher rates of depression and anxiety. It is therefore possible that latent and unassessed dimensions such as depression, or anxiety, might have biased two or more dimensions in the same or opposite direction. Fourth, the immobilization test [60] or L-dopa test [61] would have provided a more reliable diagnosis of RLS. However, such tests are demanding in terms of cost, procedure and laboratory staff. Furthermore, so far as we know these tests have not yet been employed to assess RLS in samples as large as in the present study. Fifth, a longitudinal or interventional study design would have allowed observation of changes and stability in sleep

and disease over time. Sixth, identifying the location of lesion and the burden of such lesions might have changed the entire pattern of results.

5. Conclusions

The present pattern of results suggests that individuals with NMOSD, CIS and MS are at high risk of suffering from RLS and self-assessed risks of OSAs. Sleep disturbances, however, were unrelated to EDSS scores, fatigue, or daytime sleepiness. The results are clinically relevant, as it is possible that sleep disturbances will remain undetected in individuals with NMOSD and CIS.

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Conflict of Interest

All authors declare no conflicts of interest.

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