Restless Leg Syndrome in Different Types of Demyelinating Neuropathies: A Single-Center Pilot Study

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Objective: to determine the prevalence of restless legs syndrome (RLS) in a cohort of patients with demyelinating neuropathies.

Methods: Patients were retrospectively recruited from our cohort of different forms of demyelinating neuropathies, including chronic inflammatory demyelinating neuropathy (CIDP), Charcot-Marie-Tooth 1A (CMT1A), and hereditary neuropathy with liability to pressure palsies (HNPP) referred to our Department of Neurology in a 10-year period. The validated 4-item RLS questionnaire was used for diagnosis of RLS. All patients with RLS who fulfilled criteria underwent a suggested immobilization test to confirm the diagnosis. A group of outpatients referred to the sleep disorders unit and data from published literature were used as controls.

Results: Prevalence of RLS in demyelinating neuropathy group was higher than prevalence observed in control population ($p = 0.0142$) or in the literature data ($p = 0.0007$). In particular, in comparison with both control population and literature data, prevalence of RLS was higher in CIDP group ($p = 0.0266$ and $p = 0.0063$, respectively) and in CMT1A group ($p = 0.0312$

and $p = 0.0105$, respectively), but not in HNPP ($p = 1.000$ and $p = 0.9320$, respectively).

Conclusions: our study confirms a high prevalence of RLS in inflammatory neuropathies as CIDP and, among inherited neuropathies, in CMT1A but not in HNPP. Considering that this is only a small cohort from a single-center retrospective experience, the link between RLS and neuropathy remains uncertain, and larger multicenter studies are probably needed to clarify the real meaning of the association between RLS and neuropathy.

Keywords: Restless leg syndrome (RLS), demyelinating neuropathies, chronic inflammatory demyelinating neuropathy (CIDP), Charcot-Marie-Tooth 1A (CMT1A), hereditary neuropathy with liability to pressure palsies (HNPP), suggested immobilization test (SIT)

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Restless legs syndrome (RLS) is a sensory-motor disorder characterized by an urge to move the legs usually accompanied by unpleasant leg sensations, exacerbation of this urge with rest, relief with activity, and worsening of symptoms toward evening.^{1,2} Though it is in most cases idiopathic, secondary forms associated with other diseases are known and must be considered in the clinical workup of RLS.^{1,2} The occurrence of RLS in association with peripheral neuropathies is well known, especially with some forms of immune-mediated neuropathies and with polyneuropathies with preferential involvement of sensory fibers.³⁻⁷

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a clinically heterogeneous, immune-mediated, grossly symmetric sensory and motor neuropathy evolving as a monophasic, relapsing, or progressive disorder. It develops over more than eight weeks, distinguishing the condition from Guillain-Barré syndrome, which has an acute onset.⁸

Charcot-Marie-Tooth (CMT) disease is a clinically and genetically heterogeneous group of inherited peripheral neuropathies.⁹ According to electrophysiological findings, CMT is divided into two main subtypes: CMT1, a primarily demyelinating neuropathy with severely reduced motor nerve conduction velocities (NCV < 38 m/s), and CMT2, a primarily axonal neuropathy with normal or slightly reduced NCV.⁹

BRIEF SUMMARY

Current Knowledge/Study Rationale: Peripheral neuropathy is commonly listed as a secondary cause of restless legs syndrome (RLS); however, the prevalence estimates of RLS in neuropathies are extremely variable, and no clear association has been established with inflammatory neuropathies. Determining the real prevalence of RLS in different forms of neuropathies is extremely important for a complete clinical evaluation of patients.

Study Impact: We confirmed a high prevalence of RLS in our cohort of patients with chronic inflammatory demyelinating neuropathy (CIDP) and Charcot-Marie-Tooth 1A (CMT1A), but not in those affected by hereditary neuropathy with liability to pressure palsies (HNPP). Heterogeneous involvement of somato-sensory pathway in these types of demyelinating neuropathies may contribute to explain the different prevalence observed.

The most common form is CMT1A, due to a duplication of a 1.4 MB region containing the gene encoding the peripheral myelin protein 22 (PMP22).⁹ CMT1A discloses a stereotypical sensorimotor, length-dependent neuropathy associated with marked and homogeneous slowing of nerve conduction velocities.⁹ The deletion of the same chromosome 17 region causes hereditary neuropathy with liability to pressure palsy (HNPP), usually characterized by recurrent palsies due to trivial traumas.⁹

Figure 1—Exemplificative suggested immobilization test from a patient affected by chronic inflammatory demyelinating polyneuropathy

Periodic bursts of motor unit potentials involving all muscles examined are shown. About three minutes of continuous recording are shown. Calibration and time scale are in the lower right corner.

In this report we investigate the prevalence of RLS, using validated diagnostic criteria, in a cohort of demyelinating neuropathies, including CIDP, CMT1A, and HNPP.

METHODS

Patients were retrospectively recruited from those seen in the Departments of Neurology at our university hospital, which is a referral center for Neuropathies of Lazio region, over a 10-year period (2000-2010). Diagnosis of CIDP was formulated according to fulfilling the criteria of the European Federation of Neurological Societies/Peripheral Nerve Society.¹⁰ FISH (fluorescence in situ hybridization) analysis using BAC (bacterial artificial chromosome) clone dJ1004H15, directly labeled with Spectrum Orange-dUTP (Vysis), was performed on metaphase chromosomes and interphase nuclei of cultured peripheral blood lymphocytes to detect microdeletion or microduplication of PMP22-containing region for diagnosis of CMT1A or HNPP.¹¹

Motor and sensory nerve conduction studies of upper and lower limbs were performed using standard techniques.¹²⁻¹⁴ All studies were performed in a warm room. Skin temperature was maintained above 32°C. If needed, an infrared lamp was used to warm the studied segment.

All patients underwent extensive laboratory studies to rule out other causes of neuropathy, including fasting plasma glucose, glycosylated hemoglobin, fT₃, fT₄, TSH, anti-thyroid antibodies, serum vitamin B₁₂ and folates, hepatic enzymes, creatinine, urinalysis, immunofixation electrophoresis, anti-MAG assay, antinuclear antibodies (ANA), anti-extractible nuclear antigens, anti-DNA antibodies, antineutrophil cytoplasmic antibodies (ANCA), circulating C3 and C4, serologic tests for HBV, HCV and HIV, and screening for malignancies, malabsorption, or systemic autoimmune disorders.

For diagnosis of RLS, the validated 4-item RLS criteria were used.¹ Fulfillment of all 4 criteria was required for diagnosis; moreover, we considered positive for RLS patients who report-

ed symptoms with a frequency > 3 days per week. This was established by an unblinded face-to-face interview. RLS was considered severe in all cases on the basis of the frequency of the symptoms and the impact on sleep and everyday life.¹

As a control population, we included all outpatients referred to the sleep disorder center in the previous year for any kind of sleep disorder. All these patients underwent the same evaluation of RLS symptoms as the study population. We also compared our data with the prevalence of RLS estimated in the “REST General Population Study.”¹⁵

All patients with RLS who fulfilled criteria underwent testing of iron/ferritin serum levels and a suggested immobilization test (SIT)¹⁶ to evaluate the presence of periodic limb movements (PLM). During the test, patients remained in bed, or in an armchair reclined at a 45° angle with their legs extended. They were asked to limit their voluntary movements for the entire duration of the test. Tibialis anterior and rectus femoris muscles electromyographic (EMG) activity was monitored using surface electrodes. EMG signal was recorded with a Micromed Brain-Quick SystemPlus digital polygraph, using a band-pass filter with low-frequency = 10 Hz and high-frequency = 250 Hz; sampling rate was 512 Hz, A/D conversion 16 bit. A 50 μV sinusoidal calibration signal of approximately 1-min duration was obtained at the start of the monitoring. Scoring of PLM was obtained by simultaneously analyzing EMG tracing and video-monitoring. PLMs that occurred during generalized body movements were discarded from the analysis.¹⁶ PLMs during the SIT were scored according to established criteria.^{16,17} According to Montplaisir et al., an index of 40 leg movements/h was considered the cutoff between normal subjects and RLS patients.¹⁶

In addition to the 4-item IRLSSG questionnaire, all patients with symptoms of RLS underwent a structured clinical interview, which was performed in the sleep laboratory, immediately before the SIT. In this way, all conditions resulting possible RLS “mimics” (such as neuroleptic-induced akathisia, nocturnal leg cramps, positional discomfort, volitional movements,

painful conditions, both neurological or non-neurological, such as myelopathy, radiculopathy, neuropathic pain, lower limb arthritis, and nighttime pain in the lower limbs in the course of congestive heart failure) were carefully ruled out.¹⁸

Prevalence of RLS symptoms among the study population and controls were compared by means of Fisher exact test or χ^2 with Yates correction. Level of significance was set at $p < 0.05$.

RESULTS

Fifty-five neuropathic patients were enrolled: 26 with CIDP, 14 with CMT1A, and 15 with HNPP. The mean age at time of inclusion in this study was 49.6 ± 15.3 (range 16-80) years. The mean age was 52.2 ± 16.1 (range 16-74) for CIDP, 50.4 ± 12.0 (range 28-75) for CMT1A, and 45.7 ± 16.9 (range 18-80) for HNPP. There were 29 men and 26 women (14/12 for CIDP, 8/6 for CMT1A, 7/8 for HNPP). Extensive laboratory studies proved normal in all cases.

Eleven patients (20%) were diagnosed with RLS, meeting all 4 criteria. SIT confirmed the clinical diagnosis in all cases (Figure 1). Among these patients, 6 had CIDP (6/26, 23%, 3 men and 3 women), 4 CMT1A (4/14, 28%, 1 man and 3 women), and only one HNPP (1/15, 6%, 1 man). Iron/ferritin levels were normal in all cases. In all patients with RLS, dopaminergic therapy was started; all patients reported a decrease of symptoms after the onset of drug therapy.

Among a total of 321 patients referred to our sleep disorders unit, mean age was 49.1 ± 18.6 years (range 12-87). Twenty-seven patients (8.4%) were positive for RLS (12 men and 15 women, mean age 55.4 ± 17.1 years). In all these cases, nerve conduction studies ruled out a peripheral neuropathy.

No differences in mean age and gender composition were observed between the patient population and the controls. Prevalence of RLS in the neuropathy group was higher than that observed in control population (Fisher exact test, $p = 0.0142$, $\chi^2 = 4.21$; $p = 0.040$, OR = 2.18). In particular, prevalence of RLS was higher in CIDP group (Fisher exact test; $p = 0.0266$; $\chi^2 = 6.01$; $p = 0.014$, OR = 3.27) and in CMT1A group (Fisher exact test, $p = 0.0312$; $\chi^2 = 6.49$; $p = 0.010$, OR = 4.36), but not in HNPP (Fisher exact test, $p = 1.000$; $\chi^2 = 0.06$; $p = 0.811$, OR = 0.78). No correlation was found between RLS occurrence and severity of neuropathy or nerve conduction studies. No significant differences were observed in prevalence of RLS among single groups of neuropathies.

When comparing our results with those of REST General Population Study,¹⁵ which found the RLS in 1,114 individuals out of 15,391 controls (7.2%),¹⁵ the prevalence of RLS was higher in our group of demyelinating neuropathies group (χ^2 with Yates correction, $p = 0.0007$, OR = 3.20). The prevalence of RLS was also confirmed to be higher in CIDP group (χ^2 with Yates correction, $p = 0.0063$, OR = 3.84) and in CMT1A group (χ^2 with Yates correction, $p = 0.0105$, OR = 5.13), but not in HNPP (χ^2 with Yates correction, $p = 0.6795$, OR = 0.92).

DISCUSSION

Peripheral neuropathy is commonly listed as a secondary cause of RLS. However prevalence estimates of RLS in neuropathy are extremely variable, ranging from 5.2% to 54%,

while generally, the frequency of RLS in a control population is around 7%.^{3,15} Furthermore, clinically relevant forms of RLS (forms which interfere with daily functioning) have a prevalence of 2.7%.¹⁵

On the other hand few studies have examined the epidemiology of CIDP, but its prevalence is probably underestimated because of difficulty in diagnosis of so-called atypical cases. At present, only few published studies exist showing variable results for prevalence, ranging from 1/100000 cases to 8/100000 cases.¹⁹⁻²¹

The prevalence of CMT1A is generally around 15/100000, while for HNPP the prevalence is around 7/100000.²² Considering the common genetic origin of both these inherited neuropathies, the lower prevalence of HNPP can be explained by the extremely marked clinical variability that makes this diagnosis difficult.¹¹

Some authors found a high prevalence of RLS in inherited neuropathies without any association between the disease and chronic inflammatory demyelinating neuropathy,⁴ but others have reported a possible association between RLS and CIDP.³

The neural mechanisms implicated in RLS are usually considered of central origin; iron system and dopaminergic pathway contribute to the disease pathogenesis.²³ Abnormal sensory input, as occurs in peripheral neuropathies, may play an activating role in the CNS mechanisms of the disease.^{15,24}

We evaluated the prevalence of RLS in a cohort of demyelinating neuropathies, including definite CIDP and genetically proven CMT1A and HNPP, and we compared these data with those observed in our control population. A high prevalence of the disease was observed in CIDP and CMT1A groups, but not in HNPP patients. Notably, serum levels of iron and ferritin were normal in all patients with RLS associated with neuropathies. Our data confirm previous reports, where a high prevalence of RLS in inflammatory neuropathies was established.³ We also noted, as previously described, a high prevalence of RLS in hereditary neuropathies.^{4,24}

Interestingly in this category, while the prevalence of RLS was increased in CMT1A, we did not observe any association of RLS with HNPP. We hypothesized that in CMT1A, involving impairment of all nerves—especially the longest ones of lower limbs—the dysfunction of somato-sensory pathway may contribute to RLS development. On the other hand, in CIDP, which is an inflammatory immune-mediated neuropathy, the longest lower limbs nerves may be more frequently affected by the inflammatory process. Supporting this hypothesis, the prevalence of RLS is increased in inflammatory disorders of central nervous system, such as multiple sclerosis,^{25,26} of which CIDP can be considered the peripheral counterpart, with respect to clinical (relapsing or progressive disease course), pathological (focal demyelination and concomitant axon damage), and pathogenic features.²⁷

Conversely in HNPP, where peripheral nerves are only more susceptible to external noxious stimuli, the somato-sensory pathway is generally preserved, thus explaining the absence of an increased prevalence of RLS in this condition.

RLS has been described in association with a variety of neurological disorders. In a recent review, Weinstock et al. observed that, when controlled studies were used to define a condition as a highly associated RLS condition, 95% of these

disorders have also been associated with inflammation and/or immune changes, 37% with systemic iron deficiency, 37% with peripheral neuropathy, and 32% with small intestinal bacterial overgrowth. Inflammation was most commonly associated with increased levels of proinflammatory interleukins, most commonly IL-6, but also interleukins 1, 2, 4, 12, 17, and 18.²⁸ Moreover, Parkinson disease, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer disease, and migraine are associated with RLS but have neither systemic nor CNS iron deficiency.²⁸ According to the authors, literature data raise the possibility that some of so-called idiopathic RLS could also be mediated by inflammatory and/or immunological mechanisms.²⁸

In conclusion, considering that this is only a small cohort from a single-center experience and that our study is retrospective, the link between RLS and neuropathy remains uncertain. As a further limitation of this study, we enrolled as a control population, outpatients who were referred to a sleep disorder clinic. In this way, of course, we obtained a control population in which the prevalence of RLS is likely much higher than in normal healthy controls. This could lead to an underestimation of the association between RLS and demyelinating neuropathies. For this reason, we also compared our data with the prevalence data reported in the REST General Population Study, and we obtained confirmation of all our results. Larger multi-center studies are probably needed to clarify the real meaning of the association between RLS and neuropathy.

ABBREVIATIONS

RLS, Restless leg syndrome
CIDP, chronic inflammatory demyelinating neuropathy
CMT, Charcot-Marie-Tooth
HNPP, hereditary neuropathy with liability to pressure palsies
SIT, suggested immobilization test
NCV, nerve conduction velocity
FISH, fluorescence in situ hybridization
BAC, bacterial artificial chromosome
PMP22, peripheral myelin protein 22
MAG, myelin associated glycoprotein
ANA, antinuclear antibody
ANCA, antineutrophil cytoplasmic antibodies
ENA, extractable nuclear antigens
HBV, hepatitis B virus
HCV, hepatitis C virus
HIV, human immunodeficiency virus
EMG, electromyographic examination
PLM, periodic limb movements

REFERENCES

- Allen RP, Picchiotti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir 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 Med* 2003;4:101-19.
- American Academy of Sleep Medicine. *The international classification of sleep disorders - diagnostic and coding manual*. 2nd edition. Westchester, IL: American Academy of Sleep Medicine, 2005.
- Rajabally YA, Shah RS. Restless legs syndrome in chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2010;42:252-6.
- Hattar E, Chalk C, Postuma RB. Is there a higher risk of restless legs syndrome in peripheral neuropathy? *Neurology* 2009;72:955-60.

- Boentert M, Dziewas R, Heidbreder A, et al. Fatigue, reduced sleep quality and restless legs syndrome in Charcot-Marie-Tooth disease: a web-based survey. *J Neurol* 2010;257:646-52.
- Polideffis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome. *Neurology* 2000;55:1115-21.
- Gemignani F, Vitetta F, Brindani F, Contini M, Negrotti A. Painful polyneuropathy associated with restless legs syndrome. Clinical features and sensory profile. *Sleep Med* 2013;14:79-84.
- Vallat JM, Sommer C, Magy L. Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition. *Lancet Neurol* 2010;9:402-12.
- Reilly MM, Murphy SM, Laurá M. Charcot-Marie-Tooth disease. *J Peripher Nerv Syst* 2011;16:1-14.
- Van den Bergh PY, Hadden RD, Bouche P, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society- first revision. *Eur J Neurol* 2010;17:356-63.
- Luigetti M, Conte A, Madia F, et al. A new single-nucleotide deletion of PMP22 in an HNPP family without recurrent palsies. *Muscle Nerve* 2008;38:1060-4.
- Kimura J. *Electrodiagnosis in disease of the nerve and muscle: principles and practice*. Philadelphia: FA Davis; 1989: 103-38.
- Padua L, Lo Monaco M, Aulisa L, et al. Surgical prognosis in carpal tunnel syndrome: usefulness of a preoperative neurophysiological assessment. *Acta Neurol Scand* 1996;94:343-6.
- Luigetti M, Quaranta D, Modoni A, Mereu ML, Lo Monaco M. Nerve conduction studies of the sural nerve: Normative data from a single-center experience. *Clin Neurophysiol* 2012;123:1891-2.
- Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L. Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 2005;165:1286-92.
- Montplaisir J, Boucher S, Nicolas A, et al. Immobilization tests and periodic leg movements in sleep for the diagnosis of restless leg syndrome. *Mov Disord* 1998;13:324-9.
- Zucconi M, Ferri R, Allen R, et al. The official World Association of Sleep Medicine (WASM) standards for recording and scoring periodic leg movements in sleep (PLMS) and wakefulness (PLMW) developed in collaboration with a task force from the International Restless Legs Syndrome Study Group (IRLSSG). *Sleep Med* 2006;7:175-83.
- Brindani F, Vitetta F, Gemignani F. Restless legs syndrome: differential diagnosis and management with pramipexole. *Clin Interv Aging* 2009;4:305-13.
- Chiò A, Cocito D, Bottacchi E, et al. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J Neurol Neurosurg Psychiatry* 2007;78:1349-53.
- Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J Neurol Neurosurg Psychiatry* 1999;66:677-80.
- Mygland A, Monstad P. Chronic polyneuropathies in Vest-Agder, Norway. *Eur J Neurol* 2001;8:157-65.
- Foley C, Schofield I, Egton G, Bailey G, Chinnery PF, Horvath R. Charcot-Marie-Tooth disease in Northern England. *J Neurol Neurosurg Psychiatry* 2012;83:572-3.
- Salas RE, Gamaldo CE, Allen RP. Update in restless legs syndrome. *Curr Opin Neurol* 2010;23:401-6.
- Gemignani F, Marbini A, Di Giovanni G, Salih S, Terzano MG. Charcot-Marie-Tooth disease type 2 with restless legs syndrome. *Neurology* 1999;52:1064-66.
- Aydar G, Kurt S, Karaer Unaldi H, Erkorkmaz U. Restless legs syndrome in multiple sclerosis. *Eur Neurol* 2011;65:302-6.
- Li Y, Munger KL, Batool-Anwar S, De Vito K, Ascherio A, Gao X. Association of multiple sclerosis with restless legs syndrome and other sleep disorders in women. *Neurology* 2012;78:1500-6.
- Madia F, Frisullo G, Nociti V, et al. pSTAT1, pSTAT3, and T-bet as markers of disease activity in chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2009;14:107-17.
- Weinstock LB, Walters AS, Pauksakon P. Restless legs syndrome-theoretical roles of inflammatory and immune mechanisms. *Sleep Med Rev* 2012;16:341-54.

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