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Risk factors for Lumbosacral Radiculoplexus Neuropathy

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Abstract

Introduction/Aims: Recently, our group found an association between diabetes mellitus (DM) and lumbosacral radiculoplexus neuropathy (LRPN) in Olmsted County, Minnesota; we found a higher risk (OR: 7.91) for developing LRPN in diabetic compared to non-diabetic patients. However, the influence of other comorbidities and anthropomorphic variables was not studied.

Methods: Demographic and clinical data from 59 LRPN patients and 177 age-sex matched controls were extracted using the Rochester LRPN epidemiological study. Differences between groups were compared by Chi-square/Fisher's exact test or Wilcox sum rank. Univariate and multivariate logistic regression analysis were performed.

Results: Factors predictive of LRPN on univariate analysis were DM (OR 7.91; CI 4.11-15.21), dementia (OR 6.36; CI 1.13-35.67), stroke (OR 3.81; CI 1.32-11.01), dyslipidemia (OR 2.844; CI 1.53-5.27), comorbid autoimmune disorders (OR 2.72; CI 1.07-6.93), hypertension (OR 2.25; CI 1.2-4.13), obesity (OR 2.05; CI 1.11-3.8), BMI (OR 1.1; CI 1.04-1.15), and weight (OR 1.02; CI 1.009-1.037). On multivariate logistic regression analysis only DM (OR 8.03; CI 3.86-16.7), comorbid autoimmune disorders (OR 4.58; CI 1.45-14.7), stroke (OR 4.13; CI 1.2-14.25) and BMI (OR 1.07; CI 1.01-1.13) were risk factors for LRPN.

Discussion: DM is the strongest risk factor for the development of LRPN, followed by comorbid auto-immune disorders, stroke and higher BMI. Altered metabolism and immune dysfunction seem to be the most influential factors in the development of LRPN.

Keywords

vasculitis; lumbosacral radiculoplexus neuropathy; lumbosacral plexopathy; diabetes mellitus

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Ethical Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Introduction

Lumbosacral radiculoplexus neuropathy (LRPN) is an immune-mediated neuropathy characterized by unilateral or asymmetrical lower limb weakness, pain, prickling, and sensory loss.[1] Initially, it was thought to occur only in people with diabetes mellitus (DM) (DLRPN), but a similar disorder can also affect people without DM, known as non-diabetic LRPN (NDLRPN).[2,3] Recently, we found a significantly higher occurrence of DM in LRPN patients compared to age-sex matched controls (66.1% vs. 19.8%) from Olmsted County, Minnesota, USA.[4] Within the same population, we found that people with DM have an odds ratio of 7.91 for developing LRPN compared to non-diabetics[4] and that the survival is reduced compared to controls (mostly secondary to DM).[5]

The pathophysiology of LRPN is still not fully elucidated. Several pathological studies have shown evidence of ischemic injury and microvasculitis of nerve and up-regulation of inflammatory mediators in nerves of patients with LRPN,[6,2,7-9] which makes LRPN a variant of non-systemic vasculitic neuropathy.[10] DM is a definite risk factor, but how DM triggers an auto-immune attack to roots, plexus and nerves is still largely unknown. In addition, the influence of anthropomorphic variables or other comorbidities on LRPN has not yet been studied.

Herein we investigate the risk factors for LRPN in a population-based setting from Olmsted County, Minnesota.

Methods

Demographic, anthropomorphic, laboratory and clinical data from LRPN patients and controls were extracted from the Olmsted County LRPN epidemiological study, in which the incidence of LRPN was recently determined.[4] The study design, LRPN inclusion and exclusion criteria and controls identification can be found in supplementary table 1.[4] Each case of LRPN was matched with three non-LRPN patients by age and sex. In people with LRPN, data were extracted from the time of diagnosis. In the control group, data were extracted from the closest medical visit or laboratory study within one year of the matched-LRPN diagnosis date. This study was approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

Anthropomorphic variables

The metrics used were standard international. Overweight and obesity were defined by body mass index (BMI) > 25 and > 30 kg/m2 respectively.

Medical Comorbidities

Diabetes Mellitus—The diagnosis of DM was according to American Diabetes Association criteria.[11] Duration of DM, presence of microvascular complications, and amputation were extracted from medical records.

Other comorbidities—History of hypertension, dyslipidemia, heart failure, coronary artery disease, stroke, non-skin-cancer, chronic kidney disease (CKD), dementia, peripheral

artery disease, and comorbid autoimmune disorders was extracted from problem list diagnostic index or medical notes.

Statistical Analysis

Categorical variables were summarized using frequencies and percentages and groups were compared using χ^2 and Fisher's exact tests as appropriate. Continuous variables are presented as median and range, and groups were compared using Wilcoxon rank sum test. Association between LRPN and risk factors were accessed using univariate and multivariate logistic regression with odds ratios (OR) reported. A two-tailed a priori alpha level of <0.05 was considered significant. Statistical analysis were performed using SAS® (version 9.4, SAS Institute, Cary, NC) and JMP (pro version 15.0, SAS Institute, Cary, NC).

Results

LRPN versus controls

Fifty nine LRPN patients and 177 age-sex matched controls were identified. Compared to controls, LRPN patients more frequently had: hypertension, DM,[4], obesity, dyslipidemia, stroke, dementia, and comorbid autoimmune disorder (table 1). Patients with LRPN had a higher BMI and a higher weight compared to the control group (table 1). In the LRPN group, 9 patients had 11 comorbid autoimmune disorders (2 patients had 2 comorbid autoimmune disorders): autoimmune thyroiditis (n=4), inflammatory bowel disease (n=2), type 1 DM (n=2), myasthenia gravis (n=1), multiple sclerosis (n=1), and psoriasis (n=1).

DLRPN versus diabetic controls

In patients with DM, DM duration, fasting glucose, BMI, weight, microvascular DM complications, or frequency of any other comorbidity were similar between DLRPN and diabetic controls (table 2).

NDLRPN versus non-diabetic controls

In non-diabetic patients, the frequency of stroke and dyslipidemia were higher in the LRPN group (table 2) versus non-diabetic controls. No other comorbidity or anthropomorphic variable was different between groups.

Risk factor analysis

On univariate logistic regression analysis, DM,[4] dementia stroke, dyslipidemia, comorbid auto-immune disorders, hypertension, obesity, BMI, and weight, were predictive factors for the development of LRPN (table 3). On multivariate logistic regression analysis, only DM, comorbid autoimmune disorders, stroke and BMI remained as risk factors for LRPN (table 3).

Discussion

In this study, we demonstrate that hypertension, stroke, obesity, dementia, dyslipidemia, and comorbid autoimmune disorders are more frequent in patients with LRPN than age-sex matched controls. Many of these variables are part of the metabolic syndrome. This adds

to our previous study within the same population,[4] which showed that DM frequency is higher in the LRPN population[4] and that survival is reduced.[5] In people with DM, the odds for developing LRPN are increased approximately 8-fold. On multivariate analysis, we now show that DM is the strongest risk factor for the development of LRPN, followed by a history of comorbid autoimmune disorders, stroke, and higher BMI. This suggests that there were no unmeasured confounding factors in our previous study and that DM is the most important risk factor for developing LRPN.

The pathogenic processes that trigger LRPN are not known. DM (chronic hyperglycemia) may induce neuronal damage by several mechanisms, including the formation of advanced glycation end-products, increased oxidative stress, mitochondrial dysfunction, and activation of the polyol and hexosamine pathways.[12] Rapid glycemic changes may lead to neuronal apoptosis due to glucose deprivation and microvascular neuronal damage due to recurrent hypoglycemia.[13] Hyperlipidemia induces excessive fatty acid oxidation, which generates reactive species of oxygen and systemic and local inflammation via macrophage activation with subsequent cytokine and chemokine production; this may injure the peripheral nervous system, especially the Schwan cells.[14] Several studies have found positive associations between serum markers of inflammation, lipid metabolism, and onset and progression of complications in individuals with type 1 and type 2 DM.[15] Metabolic syndrome and DM are associated with the accumulation of neurotoxic deoxysphingolipids that may induce neuronal apoptosis.[16] Although none of the these mechanisms seem to directly cause LRPN, we postulate that metabolic-mediated peripheral nerve injury may trigger an inflammatory response against roots, plexus and nerves, manifesting as LRPN. This may relate to rapid glycemic change as can occur in DLRPN and as has been shown to occur in treatment-induced diabetic neuropathy.[17]

We found that comorbid autoimmune disorders are risk factors for the development of LRPN. The comorbid autoimmune conditions most commonly encountered were autoimmune thyroiditis, inflammatory bowel disease, and type 1 DM. It is unclear if type 1 DM is a risk factor because of the diabetic state or because of its autoimmune pathogenesis. Genetic predisposition is likely to play a role in autoimmunity, which may explain autoimmune disorders co-occurring within individuals and families.[18] HLA is the most reported genetic factor associated with several autoimmune diseases, being the most associated with type 1 DM, rheumatoid arthritis, celiac disease, ankylosing spondylitis, and multiple sclerosis.[19] History of stroke and obesity (increased BMI) are also risk factors for LRPN after multivariate analysis. We think these findings strengthen our hypothesis that metabolic factors and the metabolic syndrome play a role because people with stroke frequently have hypertension, DM, obesity, poor diet, sedentarism, and dyslipidemia.[20] Patients with LRPN may share a particular genetic predisposition for developing this neuropathy when challenged by these metabolic factors. The higher median BMI(31.8 vs 25.7[6] and 25.1[2] kg/m^2) and less frequent weight loss (>10 lbs)(32.2% vs 77.8%) in the community LRPN cohort compared to referral-LRPN cohorts likely reflectsdifferences among these cohorts, with more severe disease occurring in the referral-cohorts.[5]

There was no significant difference among anthropomorphic variables, comorbidities, DM complications, DM duration, or laboratory findings between DLRPN patients and controls

with DM. Compared to a DLRPN referral-based cohort,[6] the median duration of DM was longer in our community-based LRPN cohort (8.5 vs. 4.1 years), but the median HbA1c was essentially the same (7.6% vs. 7.5%). Even though our study sheds some light on possible risk factors for LRPN, it is still unclear what particular characteristics a person with DM may have that causes them to develop LRPN.

Our study has some limitations. The major limitation is its retrospective nature (case-control design) that did not allow us to investigate if rapid glycemic change, surgery, weight loss, change in exercise routine, dietary habits or infections are risk factors for LRPN. Also, most of the comorbidities were extracted from clinical notes or problem list diagnostic indices rather than directly from laboratory or other clinical data and so the results may have been less accurate.

Conclusion

We find that DM is the largest risk factor for the development of LRPN, followed by comorbid autoimmune disorders, stroke, and higher BMI. Altered metabolism and immune dysfunction seem to be the most influential factors in the development of this immune-mediated neuropathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
DLRPN	diabetic lumbosacral radiculoplexus neuropathy
DM	diabetes mellitus
LRPN	lumbosacral radiculoplexus neuropathy
NDLRPN	nondiabetic lumbosacral radiculoplexus neuropathy
REP	Rochester Epidemiology Project

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Table 1-

Comparison of comorbidities and anthropomorphic variables between patients with LRPN and controls

Variables	LRPN n=59		Controls n=177		p
	Yes, N	%	Yes, N	%	
Hypertension	38	64	79	45	**0.009**
Diabetes Mellitus	39	66	35	20	**<0.001**
Obesity	30	51	59	33	**0.021**
Dyslipidemia	39	66	72	41	**<0.001**
CKD	9	15	18	11	0.288
Stroke	8	14	7	4	**0.009**
Heart failure	5	8	14	8	0.890
CAD	18	31	34	19	0.07
PAD	1	2	6	3	0.506
Dementia	4	7	2	1	**0.017**
Comorbid autoimmune disorder	9	15	11	6	**0.031**
Cancer	15	25	35	20	0.356
	Median	**range**	**Median**	**range**	
BMI, kg/m^2	31.4	18.4-57.5	28	16.1-47.7	**<0.001**
Weight, kgs	90.3	53-172	79.6	37.8-181	**<0.001**
Height, cms	171	135-188	168	98.9-196	0.36

LRPN- lumbosacral radiculoplexus neuropathy; CKD- chronic kidney disease; CAD- coronary artery disease; PAD- peripheral artery disease; BMI- body mass index; kgs- kilograms; cms- centimeters

Table 2-

Comparison of comorbidities and laboratory and anthropomorphic variables in diabetic (LRPN vs controls) and non-diabetic (LRPN vs controls) patients

Variables	**Diabetic LRPN n=39**		**Diabetic Controls n=35**		**p**
	Yes, N	**%**	**Yes, N**	**%**	
Diabetic microvascular complications	18	46	16	46	0.887
Amputation	2	5	1	3	0.621
Hypertension	28	72	26	74	0.81
Dyslipidemia	27	69	24	69	0.951
Stroke	4	10	3	9	0.805
Obesity	24	62	17	49	0.276
Dementia	3	8	1	3	0.358
Comorbid auto disorder	6	15	2	6	0.181
	Median	**range**	**Median**	**range**	
DM duration, years	8.5	0-41	10	1-50	0.753
Fasting glucose, mg/dl	163	41-430	143	99-291	0.409
HbA1c, %	7.6	5.2-12.5	6.6	5.4-10.7	0.074
BMI, kg/m^2	33.3	18.4-57.5	31.2	16.1-47.7	0.132
Weight, kgs	98	53-172	85	42-152	0.072
Variables	**Non-diabetic LRPN n=20**		**Non-diabetic Controls n=142**		**p**
	Yes, N	**%**	**Yes, N**	**%**	
Hypertension	10	50	53	37	0.323
Pre-diabetes	10	50	55	38.7	0.336
Dyslipidemia	12	60	48	34	**0.028**
Stroke	4	20	4	2.8	**0.009**
Obesity	7	35	47	33	0.965
Dementia	1	5	1	1	0.232
Comorbid auto disorder	3	15	9	6	0.171
	Median	**range**	**Median**	**range**	
BMI, kg/m^2	29.4	21.0-52.1	27.4	16.1-46.2	0.345
Weight, kgs	87	53-140	79	38-181	0.35

LRPN- lumbosacral radiculoplexus neuropathy; DM- diabetes mellitus; Comorbid auto disorder- comorbid autoimmune disorder; BMI- body mass index; kgs- kilograms.

Table 3-

Risk factors for Lumbosacral Radiculoplexus Neuropathy

UNIVARIATE LOGISTIC REGRESSION			
Variables	**OR**	**95% CI of OR**	
Sex	1.122	0.619	2.035
Age	1.002	0.982	1.023
BMI	**1.095**	**1.044**	**1.148**
Weight	**1.023**	**1.009**	**1.037**
Height	1.012	0.985	1.04
Overweight	1.935	0.845	4.434
Obesity	**2.053**	**1.111**	**3.796**
Chronic Kidney Dysfunction	1.59	0.672	3.762
Hypertension	**2.245**	**1.22**	**4.13**
Diabetes	**7.911**	**4.114**	**15.211**
Pre-diabetes	1.006	1.004	1.012
Coronary artery disease	1.846	0.946	3.603
Heart failure	1.078	0.371	3.132
Amputation	6.173	0.55	69.346
Stroke	**3.81**	**1.318**	**11.013**
Dementia	**6.362**	**1.134**	**35.673**
Peripheral artery disease	0.491	0.058	4.167
Dyslipidemia	**2.844**	**1.535**	**5.27**
Cancer	1.383	0.692	2.766
Comorbid Autoimmune disorder	**2.716**	**1.065**	**6.926**
MULTIVARIATE LOGISTIC REGRESSION			
Variables	**OR**	**95% CI of OR**	
BMI	**1.068**	**1.011**	**1.129**
Diabetes	**8.029**	**3.86**	**16.7**
Stroke	**4.128**	**1.195**	**14.257**
Comorbid autoimmune disorder	**4.61**	**1.446**	**14.696**

LRPN- lumbosacral radiculoplexus neuropathy; OR- odds ratio; CI- confidence interval; BMI- body mass index. $p<0.05$ are shown en bold.