Lumbosacral radiculoplexus neuropathy

Incidence and the association with diabetes mellitus

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Abstract

Objective

To determine the previously unknown incidence of lumbosacral radiculoplexus neuropathy (LRPN) and its association with diabetes mellitus (DM).

Methods

LRPN defined by clinical and electrophysiologic criteria was identified among Olmsted County, Minnesota, residents during a 16-year period (2000–2015) using the unique facilities of the Rochester Epidemiology Project. DM was ascertained using American Diabetes Association criteria.

Results

Of 1,892 medical records reviewed, 59 patients (33 men, 26 women) were identified as having LRPN. The median age was 70 years (range 24–88 years) and the median time of onset of symptoms to diagnosis was 2 months (range 1–72 months). DM was more frequent in patients with LRPN than in controls (39/59 vs 35/177, $p < 0.001$) but not in those with pre-DM (10/20 vs 55/142, $p = 0.336$). LRPN recurred in 3 patients with DM resulting in 62 LRPN episodes during the study period. The overall incidence of LRPN was 4.16/100,000/y (95% confidence interval [CI] 3.13–5.18). The incidences of LRPN among DM and non-DM groups were 2.79/100,000/y (95% CI 1.94–3.64) and 1.27/100,000/y (95% CI 0.71–1.83), respectively. The odds of LRPN among patients with DM and pre-DM was 7.91 (95% CI 4.11–15.21) and 1.006 (95% CI 1.004–1.012), respectively.

Conclusions

LRPN incidence in Olmsted County of 4.16/100,000/y makes LRPN a common inflammatory neuropathy and is higher than that of other immune-mediated neuropathies (acute or chronic inflammatory demyelinating polyradiculoneuropathy, brachial plexus neuropathy) assessed within the same population. DM is a major risk factor for LRPN and thus justifies the continued classification of LRPN into diabetic and nondiabetic forms.

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Glossary

CI = confidence interval; DLRPN = diabetic lumbosacral radiculoplexus neuropathy; DM = diabetes mellitus; LRPN = lumbosacral radiculoplexus neuropathy; REP = Rochester Epidemiology Project.

Inflammatory lumbosacral radiculoplexus neuropathy (LRPN) is a clinical entity characterized by the pathologic hallmark of microvasculitis with resultant ischemic nerve injury.^{1–6} It is a monophasic illness that typically presents as an acute or subacute motor-predominant painful lower limb neuropathy that begins focally and unilaterally with involvement of proximal or distal segments. Contralateral LRPN, concomitant or subsequent thoracic radiculopathy, and/or cervical radiculoplexus neuropathy can occur in some patients.^{3,5,7} Patients often improve, although recovery is frequently protracted and incomplete. Recurrent attacks occur but are uncommon.

Since Bruns, Auché, and Garland's description of the diabetic variety of LRPN (DLRPN) more than 100 years ago, the association between diabetes mellitus (DM) and LRPN has been assumed in reports of the disease condition but has not been rigorously tested.^{8–10} The nondiabetic form (non-DLRPN) was not identified as a separate disease entity until 1981.¹¹ Recent studies assessing large cohorts comparing DLRPN with non-DLRPN found similar clinical, laboratory, pathologic findings, and clinical outcomes,^{4–6} making it unclear whether DM is a disease association or a true risk factor for this neurologic syndrome. Incidence studies of LRPN among DM and non-DM populations are needed to clarify this association. Unfortunately, there is scarce epidemiologic data and inadequate assessment of the risk covariates for the disorder. The only available information comes from the Rochester Diabetic Neuropathy Study, which approximates the prevalence of DLRPN to be 1% of the diabetic community but does not address the incidence of non-DLRPN.¹²

Thus, in the present study, we estimate the incidence of LRPN and then examine the frequency of DM in LRPN as compared with a geographically defined general community population by utilizing the facilities of the Rochester Epidemiology Project (REP).

Methods

Special data resource

Medical care for the residents of Olmsted County (especially for patients with neuromuscular disease) is provided almost exclusively by one medical facility (Mayo Clinic) and its 2 affiliated hospitals. All medical records of each patient are entered into a single record, an accessible master index for all diagnoses (including pathologic diagnoses and surgical procedures). The REP supports a medical records linkage system for other Olmsted County facilities providing medical care for patients not medically evaluated at the Mayo Clinic.¹³ This

comprehensive computerized medical record linkage system captures the medical records of almost the entire Olmsted County population except for a small proportion of the population (approximately 5%) who do not allow their medical records to be assessed for research purposes.¹⁴ The REP affords easy retrieval of the preserved original medical records thus allowing opportunities to study diseases in a well-circumscribed population over a long period.

Standard protocol approvals, registrations, and patient consents

Approvals for conduct of the study were obtained from the institutional review boards of Mayo Clinic and Olmsted Medical Center.

Identification of cases

All cases of possible LRPN during a 16-year period (from January 1, 2000, through December 31, 2015) with an Olmsted County address were ascertained using the central diagnostic index at Mayo Clinic and the REP. Potential patients were identified using the following disease categories: polyradiculopathy, polyradiculoneuropathy, lumbar plexopathy, lumbosacral plexopathy, lumbosacral radiculoplexus neuropathy, diabetic lumbosacral plexopathy, proximal diabetic neuropathy, diabetic amyotrophy, and diabetic mononeuritis multiplex. Cases were required to have an Olmsted County address for at least 1 year before the diagnosis of LRPN to exclude any patients moving to the area for tertiary medical care.

The following criteria were required to make the diagnosis of LRPN:

1. Clinical findings. History and neurologic examination characteristic of LRPN, i.e., an acute, subacute, or subacute to chronic onset of weakness, pain, prickling, or numbness in the lower limbs. The initial symptoms usually began focally and unilaterally and involved proximal (buttock, hip, or thigh) and/or distal (leg or foot) lower limb segments. Over time, the disease could spread to involve both proximal and distal segments and bilateral lower extremities. The neurologic examination should reveal motor, reflex, or sensory abnormalities beyond the distribution of a single root level or a single peripheral nerve.
2. Clinical neurophysiology. Electrophysiologic testing (nerve conduction and EMG) confirmed an axonal process with lumbosacral segments involvement from at least 2 different root levels and from at least 2 different peripheral nerves. Paraspinal denervation is frequently present.

3. Subspecialty assessment. All patients have been evaluated by a neurologist to make a confirmatory diagnosis of LRPN. As part of this evaluation, other causes of the lumbosacral syndrome were excluded through imaging (CT or MRI) or laboratory testing.

Patients were grouped into definite and probable LRPN categories. Patients were considered “definite” if they fulfilled all 3 criteria and “probable” if they fulfilled criterion 1 or 2 and 3. All patients’ medical records were reviewed by 2 authors (P.S.N. and P.J.B.D.), and to be included, both authors had to agree.

Exclusion criteria

Patients who met the above criteria but had structural causes such as large disks, tumor, masses, hematoma, dural arteriovenous fistula, or trauma as a potential alternative diagnosis to explain their deficits were excluded. Patients with other etiologies accounting for lumbosacral plexopathy, such as infection, radiation, multifocal chronic inflammatory demyelinating polyradiculoneuropathy, and sarcoidosis, were also excluded.

Selection of non-LRPN control patients

Three non-LRPN control patients living in Olmsted County were matched to each patient with LRPN based on age and sex. This control group served as a reference cohort for the occurrence of DM or impaired glycemia. We required that control cases be registered at Mayo Clinic or at Olmsted County Medical Center in the year (± 1) that the case met criteria for LRPN (i.e., the index date). Control cases were of the same sex and birth year (± 1) as the patient with LRPN to which they were matched and were residing in Olmsted County as of the index date.

Determination of DM status

The medical records of patients with LRPN and controls were reviewed to identify those with prevalent DM. Persons were defined as having DM if they had ongoing treatment with an antidiabetic medication for DM, coded diagnosis of DM in the medical record, or met any of the following American Diabetes Association criteria on or before the index date: A1c $\geq 6.5\%$ or a fasting plasma glucose ≥ 126 mg/dL or a 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test or a random plasma glucose of ≥ 200 mg/dL in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis.¹⁵

Statistical method

Incidence rates of LRPN were estimated by using an in-house SAS macro with the number of LRPN patient as numerator and total person-years at risk as denominator. Census data for the Olmsted County population with interpolation for intercensal years were used to estimate person-years.¹⁶ The rates were directly age- and sex-adjusted to the population structure of white persons in the United States in 2010 reflecting the demographics of Olmsted

County, MN. Standard errors and 95% confidence intervals (CIs) were calculated under the Poisson distribution. To elucidate the disease trend over time, incidence rates were estimated using number of patients in 4-year block time periods (2000–2003, 2004–2007, 2008–2011, and 2012–2015). A log-linear model for count data was used to detect the trend in age- and sex-adjusted incidence of LRPN. After case identification, a case-control approach to assess the prevalence of DM was undertaken. Categorical variables are presented as n (%) and differences between groups were compared using χ^2 /Fisher exact test. Continuous variables are summarized as mean $\pm$ SD and comparison between the groups was done using the Kruskal-Wallis test. Univariate logistic regression was used to assess the association between LRPN and DM.

Data availability

Fully anonymized data will be shared by request from any qualified investigator.

Results

Using our broad diagnostic survey in the 16-year collection period, we identified 1,892 potential LRPN cases in Olmsted County, where 59 cases (52 definite and 7 probable) met our criteria for LRPN. Of this selected group, 33 were men and 26 were women. The median age at diagnosis was 70 years (range 24–88 years). Three patients had a second episode of LRPN after having recovered or recovering from the initial episode, therefore yielding a total of 62 episodes of LRPN in the study period. The overall annual incidence of LRPN in our population adjusted for age and sex was 4.16 per 100,000 (95% CI 3.13–5.18) while the age- and sex-adjusted annual incidence of DLRPN was 2.79 per 100,000 (95% CI 1.94–3.14) and for non-DLRPN was 1.27 per 100,000 (95% CI 0.71–1.83). To establish the disease trend over time, we subdivided our data into 4 time periods given wide fluctuation in disease incidence on a yearly basis. The age- and sex-adjusted annual incidence of LRPN was 5.75 per 100,000 (95% CI 3.05–8.45) in 2000–2003, 4.07 per 100,000 (95% CI 1.92–6.22) in 2004–2007, 4.54 per 100,000 (95% CI 2.38–6.70) in 2008–2011, and 3.26 per 100,000 (95% CI 1.49–5.04) in 2012–2015 ($p = 0.13$ for trend in incidence of LRPN).

The majority of the patients with LRPN had DM (39, 66.1%). Of these, 3 were diagnosed with DM at presentation of LRPN. In the remaining non-DM cases, half of them had pre-DM (defined as A1c between 5.7% to 6.4% and/or fasting plasma glucose values between 100 and 125 mg/dL¹⁵) either at presentation or known prior to diagnosis of LRPN. Among the DM cases, type 2 DM predominated as only 2 cases had type 1 DM. Patients with DLRPN had a mean glycated hemoglobin value of 8.0% and a mean fasting plasma glucose of 181.5 mg/dL. In the non-DLRPN cases (20, 33.9%), the mean glycated hemoglobin level was 5.6% and the mean fasting blood glucose was 101.9 mg/dL (table 1).

Table 1 DM status of lumbosacral radiculoplexus neuropathy cases

	DM (n = 39)	Non-DM (n = 20)	Total (n = 59)
Diabetic state			
Type 1	2	—	
Type 2	37	—	
Pre-DM	—	10	
Mean A1c, % (SD)	8.0 (2.0)	5.6 (0.3)	
Mean fasting glucose, mg/dL (SD)	181.5 (100.7)	101.9 (12.7)	

Abbreviation: DM = diabetes mellitus.

We found the rate of DM and pre-DM to be high in the control group; 35 of 177 control patients (19.8%) had DM and 55 of the remaining 142 control patients (38.7%) had pre-DM. However, DM was still more prevalent in patients with LRPN when compared to controls (39/59 vs 35/177, $p < 0.001$) but not to those with pre-DM (10/20 vs 55/142, $p = 0.336$). The calculated univariate odds ratio of LRPN in patients with DM was 7.91 (95% CI 4.11–15.21) and the odds ratio of LRPN in patients with pre-DM was 1.006 (95% CI 1.004–1.012).

Considering the clinical features in all 62 episodes of LRPN, the median age at diagnosis was 70 years (range 24–88 years). The median time at onset of neuropathic symptoms to diagnosis was

2 months (range 1–72 months). All episodes included painful lower extremity neuropathic symptoms (57 of 62, 91.9%) except for 5 episodes (8.1%), which were painless. In 23 episodes (37.1%), bilateral lower limbs were affected by the time of initial evaluation. They were often asymmetrically involved either on neurologic examination or on electrophysiologic testing. However, 6 of these 23 episodes affected both lower limbs symmetrically. LRPN recurred in 3 patients with DM affecting the contralateral lower extremity. The time of recurrence ranged from 12 to 15 months after the initial episode.

The clinical examination pattern of lumbosacral radiculoplexus neuropathy was pure proximal segment involvement in 20 (32.3%), proximal equal to distal in 16 (25.8%), proximal greater than distal in 10 (16.1%), distal greater than proximal in 9 (14.5%), isolated distal in 4 (6.5%), and pure sensory in 3 (4.8%). Ten cases (6 DM and 4 non-DM) had either a history of or concomitant neuropathic attacks beyond the territory of the lumbosacral plexus (i.e., more widespread radiculoplexus neuropathy). Of these, 9 had thoracic radiculopathy often involving multiple levels ipsilateral to the side of the LRPN and 1 had concomitant bilateral cervical radiculoplexus neuropathy. No significant differences in clinical findings were found between the DM and non-DM groups although involvement of bilateral lower extremities was somewhat more frequent in the DM group (table 2).

Discussion

Our study systematically surveyed a geographically well-defined North Central US community to determine the

Table 2 Clinical characteristics of lumbosacral radiculoplexus neuropathy episodes

	DM (n = 42)	Non-DM (n = 20)	Total (n = 62)	p Value
Male, n (%)	25 (59.5)	10 (50)	35 (56.5)	0.511
Median age (range), y	70 (36–88)	68 (24–88)	70 (24–88)	0.798
Median interval from symptom onset to diagnosis (range), mo	2 (1–72)	2 (1–6)	2 (1–72)	0.200
Unilateral presentation, n (%)	23 (54.8)	16 (80)	39 (62.9)	0.056
Pain, n (%)	40 (95.2)	17 (85)	57 (91.9)	0.220
Clinical neuropathy pattern, n (%)				
Pure proximal	13 (31)	7 (35)	20 (32.3)	
Proximal = distal	10 (23.8)	6 (30)	16 (25.8)	
Proximal > distal	10 (23.8)	0 (0)	10 (16.1)	0.890
Distal > proximal	5 (11.9)	4 (20)	9 (14.5)	
Pure distal	2 (4.8)	2 (10)	4 (6.5)	
Pure sensory	2 (4.8)	1 (5)	3 (4.8)	
Cervical/thoracic involvement	6 (14.3)	4 (20)	10 (16.1)	0.444

Abbreviation: DM = diabetes mellitus.

incidence of LRPN previously not studied and then to test whether DM is a risk covariate for its development. We ascertained the incidence of LRPN to be 4.16/100,000/y. This finding suggests LRPN is more frequent than other inflammatory neuropathies including Guillain-Barré syndrome¹⁷ (1.7/100,000/y), brachial plexus neuropathy¹⁸ (1.64/100,000/y), or chronic inflammatory demyelinating polyradiculoneuropathy¹⁹ (1.6/100,000/y) studied previously in the same population. Given that LRPN is often an episodic, monophasic illness that is active for only a few months to a year,^{3,5} we did not ascertain the prevalence of LRPN as it is less likely to reflect the magnitude of the disease. In the present survey, we found that the occurrence of DM was more frequent in LRPN; patients with DM had an 8-fold-higher risk of developing LRPN compared to those without DM. This finding was in spite of a high proportion of patients with DM (19.8%) in our control group. This high proportion of DM in the control group was not unexpected given the median age at LRPN onset was 70 years and is comparable to the latest published National Diabetes Statistics Report whereby the prevalence rate of patients with DM who were older than age 65 years in the United States was 20.8% (95% CI 18.8–23.0).²⁰

It is interesting that we did not find pre-DM to be a risk factor for LRPN when DM and pre-DM lies along the spectrum of dysregulated glucose metabolism. It appears less likely that LRPN is caused directly by glycemic factors alone. Perhaps there are other determinants that put patients with DM at risk of developing this inflammatory neuropathy. One of these factors might be the overzealous correction of hyperglycemia, which has been observed to be temporally related to many cases of DLRPN in large case series.^{3,6} This rapid glycemic control can result in an inflammatory state, which is supported by studies showing an increase in proinflammatory cytokines provoked by experimental hypoglycemia.^{21,22} Treatment-induced neuropathy of diabetes, which is a similar syndrome affecting predominantly peripheral and autonomic small fibers, is also associated with rapid lowering of blood sugar levels.²³ Another factor may be related to aberrant sphingolipid metabolism resulting in elevated plasma level of neurotoxic deoxysphingolipids in patients with DM.²⁴ Sphingolipid metabolites have recently been demonstrated to have an important regulatory role in immunity and inflammatory disorders.²⁵ Thus, one may conjecture that it is the complex interplay between glycemia and sphingolipid metabolism that potentially leads to inflammation. However, additional mechanistic studies are required to unravel the underlying pathogenic steps involved. Further study of other factors (e.g., anthropometric measurements, glycemic variation, weight changes, and other laboratory data) within this LRPN cohort is currently under way to shed light on the pathophysiology of this inflammatory neuropathy.

Our population-based study concurred with the most prior case reports and case series observation that LRPN is a predominantly monophasic illness with acute to subacute attack

of commonly painful paralytic lower limb neuropathy that usually begins unilaterally. We find that there is no significant clinical difference between the DM and non-DM groups. Only 3 of the 59 patients (5.1%) had recurrence (i.e., developed another episode of LRPN while recovering or recovered from a prior episode) and all had DM. In the majority of cases, the neurologic symptoms and signs presented in the lower limb unilaterally (39/62, 62.9%); however, progression from one lower extremity to the other resulted in bilateral, often asymmetrical involvement at initial presentation was quite common (23/62, 37.1%). The median duration from symptom onset to diagnosis of bilateral LRPN was 3 months (range 1–72 months). Although proximal segment involvement was the most common presentation at evaluation (55/62, 88.7%), distal segment involvement was also frequently observed (39/62, 62.9%).

Atypical presentations of LRPN also occurred dividing into 2 forms: sensory predominant LRPN or painless LRPN. Although uncommon, 3 patients (4.8%) presented with episodes of sensory predominant symptoms or findings clinically. However, nerve conduction studies and needle EMG proved these cases to have more widespread motor involvement of the lumbosacral plexus than the clinical examination identified. Therefore, in rare cases, acute or subacute onset of pain with isolated sensory findings (especially when present unilaterally) may be the presentation of LRPN. In these cases, careful and thorough EMG evaluation is necessary to confirm the diagnosis. Another atypical and uncommon presentation of LRPN found in our study was painless LRPN (5/62 [2 DM, 3 non-DM], 8.1%). Painless forms of DLRPN have previously been described showing the same pathology as seen in typical painful DLRPN but with a more insidious and symmetrical onset, a slower evolution, and more frequent and severe upper limb involvement.²⁶ Painless forms of non-DLRPN have not been previously described. Other nerve segments outside the lumbosacral segment were sometimes involved. Involvement of the thoracic segment (thoracic radiculopathy) was more common (9/62, 14.5%) than involvement of the cervical segment (cervical radiculoplexus neuropathy), which occurred in only 1 non-DM patient.

The strengths of our study included the following 2 factors. (1) Accurate case ascertainment as all cases of LRPN had confirmatory unequivocal neuropathic involvement as evaluated by neurologists and neurophysiologists. The assessment by the subspecialist was important as the concept of a radiculoplexus neuropathy (i.e., patchy involvement of multiple roots, plexus, and peripheral nerves) may not be familiar to some physicians. This is in part attributable to the diverse opinions formed over the years on the underlying anatomical distribution and the various descriptive terms given to the diabetic variety of this syndrome (“diabetic myelopathy,”²⁷ “diabetic amyotrophy,”¹⁰ “diabetic polyradiculopathy,”²⁸ “diabetic mononeuritis multiplex,”²⁹ “proximal diabetic neuropathy,”³⁰ “femoral or femoral-sciatic neuropathy of diabetes,”^{31,32} and “diabetic lumbosacral plexus neuropathy”³³), which may make it

difficult for the nonneurologist to diagnose LRPN. (2) Population-based study with notable data quality, reliability, and validity provided by the REP, which is detailed elsewhere.¹³ These 2 factors allowed comprehensive and systematic study of our population to provide a robust incidence rate for LRPN.

Our study had some minor limitations. We acknowledged that we might have missed cases with mild presentation of LRPN that did not result in electrophysiologic or neurologic assessment. LRPN can be more focal in some cases than the electrophysiologic requirement of involvement from 2 nerves and 2 lumbosacral nerve root distributions; however, if the criteria are loosened, then one runs a risk of including other disorders such as a structural radiculopathy or entrapment neuropathy. We might have missed rare LRPN cases with predominant cervical or thoracic radiculoplexus involvement in which the lower limb symptoms were relatively mild and could have been overlooked given the retrospective nature of our study. Given that Olmsted County, MN, is a less ethnically diverse, more highly educated and wealthier population compared to the general US population¹⁴ and that prevalence of DM is influenced by ethnicity and education,²⁰ our results might not be generalizable to some population subsets.

The results of our study are important and have implications in the care of inflammatory neuropathy. We have provided an incidence of LRPN of 4.16/100,000/y in a well-circumscribed US population. Of note, although this incidence is almost 3 times higher than that of other common inflammatory neuropathies (Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy) frequently diagnosed by neurologists, these conditions are given much more attention by physicians, scientists, and the media. The relatively common occurrence of LRPN emphasizes the ongoing need for education regarding recognition of this clinical entity and further research to better understand it. We also show compelling evidence that DM is a risk factor for the development of LRPN but not pre-DM. This finding may have significant public health care policy implication given the much larger proportion of the prediabetic population at risk of developing DM.²⁰ The high rate of DM among patients with LRPN provides justification to continue to classify this entity into diabetic and nondiabetic forms.

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Disclosure

P. Ng reports no disclosures relevant to the manuscript. P.J. Dyck previously received honoraria for his services as an associate editor of *Diabetes*. He has and continues to receive

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Peter J. Dyck, MD	Mayo Clinic, Rochester, MN	Author	Concept and design, drafting and critical revisions of manuscript, and study supervision
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