Incidence and prevalence of CIDP and the association of diabetes mellitus

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ABSTRACT

Background: The reported prevalence of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) varies greatly, from 1.9 to 7.7 per 100,000. CIDP is reported to occur more commonly in patients with diabetes mellitus (DM) but has not been rigorously tested.

Objectives: To determine the incidence (1982–2001) and prevalence (on January 1, 2000) of CIDP in Olmsted County, Minnesota, and whether DM is more frequent in CIDP.

Methods: CIDP was diagnosed by clinical criteria followed by review of electrophysiology. Cases were coded as definite, probable, or possible. DM was ascertained by clinical diagnosis or current American Diabetes Association glycemia criteria.

Results: One thousand five hundred eighty-one medical records were reviewed, and 23 patients (10 women and 13 men) were identified as having CIDP (19 definite and 4 probable). The median age was 58 years (range 4–83 years), with a median disease duration at diagnosis of 10 months (range 2–64 months). The incidence of CIDP was 1.6/100,000/year. The prevalence was 8.9/100,000 persons on January 1, 2000. Only 1 of the 23 CIDP patients (4%) also had DM, whereas 14 of 115 age- and sex-matched controls (12%) had DM.

Conclusions: 1) The incidence (1.6/100,000/year) and prevalence (8.9/100,000) of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) are similar to or higher than previous estimates. 2) The incidence of CIDP is similar to that of acute inflammatory demyelinating polyradiculoneuropathy within the same population. 3) Diabetes mellitus (DM) is unlikely to be a major risk covariate for CIDP, but we cannot exclude a small effect. 4) The perceived association of DM with CIDP may be due to misclassification of other forms of diabetic neuropathies and excessive emphasis on electrophysiologic criteria. *Neurology*® 2009;73:39–45

GLOSSARY

Az = azathioprine; **AAN** = American Academy of Neurology; **AIDP** = acute inflammatory demyelinating polyradiculoneuropathy; **CB** = conduction block; **CI** = confidence interval; **CIDP** = chronic inflammatory demyelinating polyradiculoneuropathy; **CMAP** = compound muscle action potential amplitude; **CV** = conduction velocity; **D** = distal; **DL** = distal latency; **DLRPN** = diabetic lumbosacral radiculoplexus neuropathy; **DM** = diabetes mellitus; **DPN** = diabetic polyneuropathy; **Dx** = diagnosis; **IVIg** = IV immune globulin; **LLM** = lower limit of normal; **MGUS** = monoclonal gammopathy of undetermined significance; **MM** = mycophenolate mofetil; **Mo** = monophasic; **Mtx** = methotrexate; **N** = no; **OR** = odds ratio; **P** = proximal; **Plex** = plasma exchange; **POEMS** = plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; **Pr** = progressive; **Pred** = prednisone; **RR** = relapsing-remitting; **TD** = temporal dispersion; **Y** = yes.

Chronic inflammatory demyelinating polyradiculopathy (CIDP) is a symmetric, motor greater than sensory, proximal and distal demyelinating peripheral neuropathy with a slowly progressive or relapsing course.¹ Individual reports and small case series were reported earlier,^{2,3} and in 1975, a systematic study of 53 patients detailed the natural history and electrophysiologic and pathologic features of an entity originally named *chronic inflammatory polyradiculoneuropathy*.⁴ The noted CSF protein elevation, characteristic electrophysiology, nerve pathology, and response to immunomodulation in this cohort all supported an inflammatory immune demyeli-

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nating pathophysiology. Since that time, diagnosing CIDP has largely focused on electrophysiologic criteria,⁵ with perhaps insufficient emphasis on clinical presentation.

Previously published data on the prevalence of CIDP in the general population varies greatly, with estimates ranging from 1.9 to 7.7 per 100,000,⁶⁻⁹ along with sparse reports of incidence ranging from 0.15 to 0.48.⁹⁻¹¹ The wide range of results may be attributable to differences in the clinical diagnostic criteria used, disease ascertainment, lack of information about the reference population from which the patients were drawn, and ethnic and geographic differences. Obtaining reliable information on the incidence and prevalence of CIDP is necessary to plan future research as well as to estimate the magnitude of this health problem with regard to health care needs and costs.

Here, we also ask whether the frequency of diabetes mellitus (DM) is increased in CIDP patients as compared with the general community population. Other authors have suggested that DM occurs at an increased frequency in CIDP¹²⁻¹⁶; however, confirmation based on epidemiologic study data is needed to support such an association.

METHODS Data resources. Medical care for the residents of Olmsted County (especially for neuromuscular diseases) is delivered almost exclusively by Mayo Clinic. All medical records on each patient are contained in a single file with an accessible master index for all diagnoses (including pathologic diagnoses and surgical procedures). The Rochester Epidemiology Project supports a similar record index for the other Olmsted County medical care providers for those patients not seen at the Mayo Clinic.¹⁷ The original medical records have been preserved and are easily retrieved for review.

Identification of cases. After approval from the appropriate institutional review boards, all cases of possible CIDP with an Olmsted County address over a 20-year period (from January 1, 1982, through December 31, 2001) were identified using the central diagnostic index at Mayo Clinic and the Rochester Epidemiology Project. Potential Olmsted County CIDP cases were identified using the following key words: Guillain-Barré syndrome, polyradiculitis, polyradiculoneuropathy, polyradiculopathy, CIDP, neuropathy not otherwise specified, demyelinating neuropathy, and peripheral neuropathy. Potential cases were required to have an Olmsted County address for at least 1 year before the diagnosis of CIDP to exclude any patients moving to the area for tertiary care.

We required 3 clinical criteria to be met as described in the seminal description of CIDP in 1975 by Dyck et al.⁴ to make the diagnosis of CIDP.

1. *Course.* The initial symptomatology and deficits worsen (progressive or fluctuating) over a period of time ≥ 8 weeks. The course thereafter could be progressive, monophasic, or relapsing.
2. *Nerve fiber class affected.* Preferential or at least equal involvement of large nerve fibers (motor, or vibration and proprioception) as compared with small sensory (pain and temperature) or autonomic nerve fibers.
3. *Distribution and symmetry of neuropathic involvement.* The pattern of functional involvement was that of a symmetric (less than 25% difference between sides) polyradiculoneuropathy. Included cases could be predominantly proximal or predominantly distal but had to have some degree of both to be included, with 4-limb involvement by symptoms or signs. Hyporeflexia or areflexia should be present.

Only if all 3 of these clinical features were met were electrophysiologic data reviewed. The electrophysiologic abnormalities were required to reflect a chronic polyradiculoneuropathy with features of demyelination as defined by the Mayo EMG laboratory.¹⁸ Demyelinating conduction velocities were defined as motor conduction velocity (CV) $< 70\%$ of the lower limit of normal (LLN) with an amplitude $> 50\%$ of the LLN, or a CV $< 50\%$ of the LLN with an amplitude $< 50\%$ of the LLN. A distal latency was considered prolonged if $> 150\%$ of the LLN. Conduction block was defined as a $> 50\%$ decrease in proximal compound muscle action potential amplitude (CMAP) compared with distal CMAP amplitude, regardless of distance or CMAP duration. If the distance was 10 cm or less, the CMAP difference should be $> 20\%$ to be called a conduction block. Temporal dispersion was identified if CMAP duration exceeded 130% of the LLN. F waves were considered prolonged if > 4 msec beyond the F estimate in the upper extremity and > 5 msec beyond the F estimate in the lower extremity.¹⁹

To ensure inclusion of all clinical cases of CIDP, we deemed electrophysiologic criteria for CIDP to be met if 1) conduction block or temporal dispersion was seen in at least one motor nerve, and in at least one other motor nerve there were at least 2 of the following 3 demyelinating features: prolonged F waves, prolonged distal latency, or demyelinating conduction velocity; or 2) no conduction block or temporal dispersion was seen, but in at least 2 separate motor nerves there were 2 of the 3 demyelinating features outlined previously. We also examined the electrophysiologic features of the patients who met our clinical criteria using the American Academy of Neurology AIDS Task Force CIDP electrophysiologic criteria (hereafter, AAN criteria).⁵

Laboratory studies, pathologic findings, and response to immunosuppressive therapy were considered supportive features for the diagnosis of CIDP. If a CSF analysis was performed, a CSF protein level ≥ 60 mg/dL with leukocyte count ≤ 10 cells/ μ L was considered supportive of the diagnosis of CIDP. For a nerve biopsy to be considered supportive, the histologic findings should show an inflammatory demyelinating process characterized by epineurial or endoneurial inflammation, demyelination, onion bulbs, or edema. A positive treatment response as interpreted by the treating neurologist to prednisone, methylprednisolone, IV immunoglobulin, plasma exchange, or chemotherapeutics would provide further evidence for the diagnosis of CIDP.

Exclusion criteria. People were excluded if they had other known causes of neuropathy, including inherited neuropathies, multifocal motor neuropathy (with or without conduction block), paraneoplastic disorders, lymphoma, osteosclerotic or multiple myeloma, POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes), Castleman syndrome, HIV, major immune diseases of kidney or bowel, necrotizing vasculitis, a

known or suspected metabolic deficiency or toxic condition that might cause neuropathy, Lyme disease, immune sensory and autonomic neuropathies, presence of hepatitis C, or cryoglobulins. Because some neurologists consider patients with monoclonal gammopathy of undetermined significance (MGUS)—associated peripheral neuropathy distinct from CIDP, we performed our analysis with and without these patients. Because we were evaluating the association between CIDP and DM, we did not exclude patients with DM. Persons who were not evaluated by a neurologist were excluded based on the assumption that clinical involvement must have been too temporary or too mild.

Patients were then grouped into definite, probable, and possible CIDP categories. Patients were considered “definite” if they fulfilled all clinical and electrophysiologic criteria and “probable” if they fulfilled all clinical criteria and at least one of the pathologic, laboratory, or treatment response criteria. If a patient met all clinical criteria and had demyelinating features that did not fully meet our electrophysiologic criteria, they were also considered “probable” cases. “Possible” patients were those who met all clinical criteria but did not have any supportive electrophysiologic, pathologic, laboratory, or treatment response features. All possible and probable cases were reviewed by 2 authors (R.S.L., P.J.B.D.), and the nerve biopsies were reevaluated (P.J.B.D.).

Once the CIDP cases were identified, we matched 5 non-CIDP community controls to each CIDP case. We required that control cases be registered at Mayo Clinic in the year (± 1) that the case met criteria for CIDP (i.e., the index date). Controls were of the same sex and birth year (± 1) as the CIDP case to which they were matched and were residing in Olmsted County as of the index date. The medical records of cases and controls were then reviewed to identify those with prevalent DM. Persons were defined as having DM if they met any of the following criteria before the index date: clinical diagnosis of DM, treatment with antidiabetic medication, 2 or more fasting blood sugar values ≥ 126 mg/dL, 2 or more nonfasting blood sugar values ≥ 200 mg/dL, or a coded diagnosis of DM in the medical record.

Statistical methods. Incidence rates of CIDP were estimated using an in-house SAS macro system assuming the entire population of Olmsted County in 1982–2001 to be at risk.²⁰ This time frame was subdivided into 4 blocks to elucidate any bias due to the relative “newness” of this disease. Standard errors and 95% confidence intervals (CIs) were calculated for the rates assuming that they followed a Poisson distribution. The rates were directly age- or age- and sex-adjusted to the population structure of white persons in the United States in 2000 reflecting the demographics of Olmsted County. The analysis was performed with and without patients with MGUS. Similar methods were used to estimate the prevalence of CIDP using the definite and probable cases identified above and still living in Olmsted County as of January 1, 2000. After case identification, a case-control approach to assess the prevalence of DM was undertaken. A univariate odds ratio (OR) was estimated from a logistic regression model.

RESULTS We identified 1,581 potential CIDP cases in Olmsted County using our broad diagnostic screen in the 20-year collection period, of whom 23 cases (19 definite, 4 probable, 0 possible) met our criteria for CIDP (table). Of these, 10 were female and 13 were male. The median age at diagnosis was 58 years (range 4–83 years), with 1 child and 22

adults. The median symptom duration before presentation was 10 months (range 2–64 months).

Only 1 case with definite CIDP had DM (case 10). Two cases with definite CIDP had MGUS (cases 7 and 9). The clinical course was progressive in 6, monophasic in 7, and relapsing–remitting in 10. The polyradicular pattern was proximal equal to distal segmental involvement in 12, distal greater than proximal in 10, and proximal greater than distal in 1. The CSF protein was absolutely elevated (>45 mg/dL) in 18 of the 20 cases tested and >60 mg/dL in 12. Electrophysiologic testing was performed in all and met our electrophysiologic criteria for demyelination in 19, but all 23 showed supportive features of demyelination. Using the AAN criteria, only 12 of 23 (54%) met electrophysiologic criteria for CIDP. Immune-modulating therapy was used in 21 of the 23 cases (91%), and all had a favorable response to treatment as interpreted by both the patient and the managing neurologist.

Four cases (4, 6, 13, and 14) underwent sural nerve biopsies. There were increased rates of demyelination and remyelination in all biopsies (figure) and borderline increased rates of axonal degeneration in 2 biopsies (cases 13 and 14). The rates of segmental demyelination, remyelination, and axonal degeneration on teased fiber preparations respectively were as follows: case 4: 6%, 26%, 1%; case 6: 17%, 22%, 1%; case 13: 4%, 25%, 4%; and case 14: 3%, 14%, 4%. Two biopsies (cases 6 and 14) showed regenerating clusters, thinly myelinated fibers, and small rudimentary onion bulbs (figure). All 4 biopsies showed small collections of epineurial perivascular inflammatory cells. Overall, all biopsies were suggestive of an inflammatory demyelinating disorder consistent with CIDP.

The annual incidence of CIDP in our population was 1.6 per 100,000 (95% CI 0.9–2.2). Excluding the 2 MGUS cases, the incidence was 1.4 per 100,000 (95% CI 0.8–2.0). To determine whether an increasing awareness of CIDP over time played any role in its diagnosis, we subdivided our data into 4 time periods. The age- and sex-adjusted annual CIDP incidence was 0.6 per 100,000 (95% CI 0–1.4) in 1982–1986, 1.3 per 100,000 (95% CI 0.2–2.4) in 1987–1991, 1.9 per 100,000 (95% CI 0.6–3.1) in 1992–1996, and 1.3 per 100,000 (95% CI 0.3–2.3) in 1997–2001. Therefore, an increasing awareness of CIDP seems not to have played a role in its diagnosis ($p = 0.28$).

On January 1, 2000, 11 patients with CIDP were alive and residing in Olmsted County, representing a prevalence rate of 8.9 per 100,000. If MGUS cases were excluded (1 case), the prevalence rate was 8.1 per 100,000. The age- and sex-adjusted prevalence

Table Clinical characteristics of patients with CIDP

Case	Sex	Age at Dx, y	Duration at Dx, mo	CIDP Dx	Clinical pattern	Clinical course	CSF protein, mg/dL*	Prolonged F waves	Slowed CV	Prolonged DL	TD or CB	Treatment	Response to treatment	DM	MGUS	AAN EMG criteria
1	M	77	24	Definite	P = D	Pr	—	N	Y	Y	Y	Pred/IVIg/Plex	Y	N	N	Y
2	F	70	2	Probable	P = D	Pr	49	N	Y	N	N	Pred	Y	N	N	N
3	M	74	3	Definite	P = D	Mo	114	Y	Y	Y	Y	Plex	Y	N	N	N
4	M	58	60	Definite	D > P	RR	74	Y	Y	Y	N	Pred/IVIg/MM	Y	N	N	Y
5	M	56	24	Definite	D > P	Pr	—	Y	Y	Y	N	Pred/Mtx	Y	N	N	N
6	F	62	12	Definite	P = D	RR	122	Y	Y	Y	Y	Pred/Plex/Az	Y	N	N	Y
7	F	58	6	Definite	D > P	Pr	89	N	Y	N	N	Plex	Y	N	Y	N
8	M	76	24	Probable	D > P	RR	—	N	Y	N	N	None	—	N	N	N
9	M	58	64	Definite	D > P	RR	70	Y	Y	N	Y	IVIg	Y	N	Y	Y
10	M	44	2	Definite	P = D	Mo	105	Y	Y	N	Y	IVIg	Y	Y	N	N
11	F	65	12	Definite	P = D	RR	96	Y	Y	Y	N	Pred/Az/IVIg	Y	N	N	Y
12	M	68	2	Definite	P = D	Mo	65	Y	Y	Y	N	Plex/IVIg	Y	N	N	N
13	M	47	2	Definite	D > P	RR	199	Y	Y	Y	Y	IVIg	Y	N	N	Y
14	F	56	10	Definite	D > P	Pr	59	Y	Y	Y	N	Pred/IVIg	Y	N	N	N
15	M	54	10	Definite	P = D	RR	59	Y	Y	Y	Y	Plex/IVIg	Y	N	N	Y
16	M	75	12	Definite	D > P	Mo	47	Y	Y	Y	Y	IVIg	Y	N	N	Y
17	M	70	3	Definite	P = D	Mo	169	Y	Y	Y	Y	Pred	Y	N	N	N
18	F	41	2	Definite	P = D	RR	25	Y	Y	Y	Y	IVIg/Pred	Y	N	N	Y
19	M	63	24	Probable	D > P	Mo	63	N	Y	N	N	None	—	N	N	N
20	F	39	6	Probable	P = D	Pr	31	N	Y	Y	Y	IVIg/Pred/Plex	Y	N	N	Y
21	F	4	15	Definite	P = D	RR	56	Y	Y	Y	Y	None	—	N	N	Y
22	F	83	3	Definite	P > D	RR	63	Y	Y	Y	N	IVIg/Pred	Y	N	N	N
23	F	22	36	Definite	D > P	Mo	200	Y	Y	Y	N	IVIg/Pred	Y	N	N	Y
Yes response								17	24	17	12		20	1	2	12
Median		58	10				67.5									

*Abnormal CSF >45 mg/dL.

Dx = diagnosis; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CV = conduction velocity; DL = distal latency; TD = temporal dispersion; CB = conduction block; DM = diabetes mellitus; MGUS = monoclonal gammopathy of undetermined significance; AAN = American Academy of Neurology; P = proximal; D = distal; Pr = progressive; N = no; Y = yes; Pred = prednisone; IVIg = IV immune globulin; Plex = plasma exchange; Mo = monophasic; RR = relapsing-remitting; MM = mycophenolate mofetil; Mtx = methotrexate; Az = azathioprine.

Figure Sural nerve biopsy from an Olmsted County patient with chronic inflammatory demyelinating polyradiculoneuropathy showing inflammatory demyelinating changes

(A) Teased fiber preparation: Multiple areas of demyelination (upper 4 fibers) and axonal degeneration (bottom fiber). (B) Semithin epoxy section, methylene blue: Small rudimentary onion bulbs (evidence of ongoing demyelination and remyelination) (arrow), myelinated fibers that are too thin for axon size (remyelination, asterisk), and regenerating clusters (arrowheads).

rate (including the MGUS case) was 10.3 (95% CI 4.2–16.4).

With regard to whether the frequency of DM is increased in CIDP, we found that 14 of the 115 control patients (12%) had prevalent DM and only 1 of the 23 CIDP cases (4%) had DM. When a univariate OR for prevalent DM in CIDP was calculated, the OR was 0.3 (95% CI 0.04–2.6). The OR remained 0.3 (95% CI 0.04–2.5) when adjusted for age, sex, and prior DM, suggesting that DM is not a major risk covariate for CIDP.

DISCUSSION This study systematically reviewed a northern US population to determine the incidence and prevalence of CIDP and to establish whether an increased prevalence of DM was observed within this group. In identifying potential CIDP cases, we emphasized the clinical presentation, as was done in the original large series of 1975 describing CIDP,⁴ and then used other characteristics, including electro-

physiologic data, as confirmatory features for the diagnosis. We, like others,^{21–24} believed that rigorous electrophysiologic criteria as the initial inclusion tool may be appropriate for therapeutic research trials but may miss clinical cases of CIDP that would skew an epidemiologic study such as ours. The observation that the AAN electrophysiologic criteria⁵ only identified 54% of our cases validates our concern and is in keeping with the experience of other authors.^{25–27} Nonetheless, we believe all our cases clinically had CIDP demonstrated by the typical clinical features, disease course, supportive laboratory and pathologic findings, response to immune modulating treatment, and demyelinating characteristics on electrophysiologic testing (table).

Furthermore, we did not want to include cases that had electrophysiologic findings consistent with a demyelinating process but clinically had a different syndrome (e.g., diabetic polyneuropathy [DPN]). From the onset, we aimed to include only patients with “classic” CIDP, having the typical, symmetric, polyradiculoneuropathy, rather than cases of focal or multifocal CIDP (e.g., Lewis–Sumner syndrome)²⁸ or a distal, sensory predominant form of CIDP (distal acquired demyelinating symmetric neuropathy).²⁹

In comparing our results with prior observations, our prevalence of 8.9 in 100,000 is higher than most. The 5-year prospective Norwegian study⁸ with a CIDP prevalence of 7.7 in 100,000 most closely aligns with our findings and patient demographics. Other prevalence studies were performed retrospectively, some using physician self-reporting and survey^{6,7,9} as their methodologic tool, with wide variance in prevalence values. Because of the possibility of incomplete reporting and excessive reliance on strict electrophysiologic criteria in these studies, they perhaps underestimate the prevalence of CIDP.

The perception exists that acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is more common and therefore more important for neurologists to recognize than CIDP. However, our incidence of CIDP (1.6) is similar to previously reported incidence of AIDP (1.7) studied within the same population³⁰ and to recent national AIDP incidence data (1.65–1.79).³¹ This observation suggests that CIDP and AIDP occur with similar incidences. Hence, CIDP is not a rare entity only seen in tertiary care centers, and general and community neurologists need to be aware of it.

Case ascertainment of CIDP is high in Olmsted County because of the unique medical practice and record keeping. Despite the retrospective nature of our study, methodologically, we were able to have virtually complete assessment of cases in the defined 20-year collection period. As a result, we were able to specifically address whether DM occurred more fre-

quently in our CIDP cohort than in age-, sex-, and calendar year-matched community controls. Our study did not demonstrate an increased prevalence of DM within our CIDP population as compared with the general population, with only 4% of our patients having DM vs 12% in our control population. Previous studies have reported finding DM associated with CIDP in 9% to 26% of patients.^{12,15,22} However, these studies were not population based and may have been subject to referral bias.

Identifying CIDP in diabetic patients can be difficult because many different types of neuropathy occur in association with DM. On one hand, some authors have suggested that CIDP patient with DM have a slightly different disease than classic CIDP with more axonal features and a lesser response to immunomodulatory therapy.¹² This observation may imply that at least some of these patients have a form of diabetic neuropathy and not CIDP. Alternatively, DPN and diabetic lumbosacral radiculoplexus neuropathy (DLRPN)³² are both known to have some demyelinating features on nerve conduction studies and may be confused with CIDP in diabetic patients, especially if the clinical presentation is not taken into account. In fact, during our review, we identified 2 patients who were initially diagnosed with CIDP but who were eventually diagnosed with DLRPN. Though DLRPN is typically a subacute, painful, asymmetric, lower-limb neuropathy³³ (in contrast to CIDP, which is usually painless and symmetric), we have recently identified a cohort of DLRPN patients who presented without pain but had the typical pathologic features of DLRPN.³⁴ One may conjecture that the alleged relationship between DM and CIDP may be partially due to cases of bilateral, painless DLRPN.

We do not have the statistical power to identify a subtle increase in the prevalence of DM in our CIDP patients; to determine whether DM is slightly increased in CIDP, larger, population-based studies need to be conducted. Given the low incidence of CIDP, this type of study may not be possible. However, our data strongly suggest that DM is not a major risk factor in the development of CIDP and that the perceived association of DM with CIDP may be due to a chance association or misidentification of other forms of diabetic neuropathy.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by J. Ransom.

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