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Article type : Original Article

Risk factors for CIDP: antecedent events, lifestyle and dietary habits. Data from the Italian CIDP database.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.14044

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Running title: risk factors in CIDP

Key words

Chronic inflammatory demyelinating neuropathy; CIDP; Epidemiology; Diet; Lifestyle, Infections; Vaccination

Abstract

Background: The role of lifestyle and dietary habits and antecedent events has not been clearly identified in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Methods: We collected information about modifiable environmental factors and antecedent infections and vaccinations in patients with CIDP included in an Italian CIDP database. Only patients who reported not having changed their diet or the lifestyle habits investigated in the study after the appearance of CIDP were included. The partners of patients with CIDP were chosen as controls. Gender-matched analysis was performed with randomly-selected controls with a 1:1 ratio between patients and controls.

Results: Dietary and lifestyle data of 323 patients and 266 controls were available. A total of 195 cases and 195 sex–matched controls were used in the analysis. Patients eating rice at least three times per week or eating fish at least once per week appeared to be at decreased risk of acquiring CIDP. Data on antecedent events were collected in 411 patients. Antecedent events within 1-42 days before CIDP onset were reported by 15.5% of the patients, including infections in 12% and vaccinations in 1.5%. Patients with CIDP and antecedent infections more often had an acute onset of CIDP and cranial nerve involvement than those without these antecedent events.

Conclusions: The results of this preliminary study seem to indicate that some dietary habits may influence the risk of CIDP and that antecedent infections may have an impact on the onset and clinical presentation of the disease.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare peripheral neuropathy that often responds to immune therapies[1]. The cause of CIDP is still unknown, even if the disease is mainly attributed to an autoimmune reactivity against nerve. Studies on other autoimmune diseases including multiple sclerosis (MS) and rheumatoid arthritis (RA)[2-4] have shown that modifiable lifestyle and environmental factors or previous infections may influence the developments and progression of the disease. In CIDP there are controversial data on the frequency and type of antecedent events or infections, with figures ranging from 10% to 33% (Table 1)[5-12]. It is also unclear whether lifestyle and dietary habits may have some role in the development of CIDP and in the different reported prevalence of the disease[11,13-17]. We took the opportunity of an ongoing database study on CIDP in Italy, to investigate whether lifestyle and dietary habits may be associated with the risk of developing CIDP and whether antecedent infections could influence the clinical presentation and course of the disease.

Materials and Methods

Study design

We implemented a web-based database on Italian CIDP patients where data from 435 patients with a diagnosis of CIDP[18] according to the EFNS/PNS criteria[19] were included. At enrolment, all eligible patients underwent a detailed clinical history, timing and distribution of neurological signs, and a number of disability scales[18]. In this study, we explored the prevalence of some lifestyle and dietary habits in patients with CIDP. Only patients who reported not having changed their diet or the lifestyle habits investigated in the study after the appearance of CIDP were included in the analysis. The same data were collected from the partners of patients with CIDP, as healthy controls. Since CIDP patients

and their partners were likely to share lifestyle and dietary habits and they resulted highly unbalanced by sex, we opted for a 1:1 sex-matching of patients with randomly-selected controls.

We also collected information about the occurrence of antecedent events within 1-42 days [20-21] before the onset of symptoms of the disease. Since we did not have a control population for this analysis, we used as reference data from other studies. We subsequently analyzed whether patients with antecedents infections had different clinical characteristics than those without these antecedent events and if they shared some clinical features with Guillain-Barré syndrome (GBS), a typical post infectious neuropathy.

All the data were included by the treating neurologist in a web-based electronic database expressly prepared by CINECA, Bologna, Italy. Informed consent was obtained from all participants at enrollment, and the study was approved by the Ethical Committee of each participating Center.

Assessment of lifestyle and dietary habits

In the absence of studies on the role of environmental factors in CIDP, we based our analysis on studies on other autoimmune diseases such as MS and RA, where antecedent infections, diet, cigarette smoking, alcohol and coffee were analyzed as possible risk factors[2-4]. Subjects were asked about their lifestyle and dietary habits using an identical structured questionnaire for patients and controls. We asked for exposure to toxic agents (prolonged vs. never/occasional) smoking (including duration and amount of exposure), illicit drugs consumption (repeated vs. never/occasional), alcohol use (including amount of exposure), dietary regimen (vegan, vegetarian, macrobiotic, omnivorous, others to be specified),

frequency of consumption of a variety of foods (1 or more time per day, 3-4 times per week, 1-2 times per week, 2-3 times per month). Items related to dietary habits included pasta, rice, meat, raw meat, white meat, fish, vegetables, fruit, cheese, eggs, sweets, coffee, tea, milk, and soft drinks.

Assessment of antecedent events

Patients were asked about the presence of an antecedent event including flu-like syndrome, upper respiratory infection, gastrointestinal infection, vaccination, surgery, trauma, and new therapy started before disease onset. We also assessed whether antecedents infections were more frequently associated with an acute clinical onset (A-CIDP), presence of autonomic symptoms, cranial nerve involvement, pain, ataxia, response to IVIg and steroid therapy. In this study, patients with A-CIDP were considered those initially diagnosed with GBS with a subsequent clinical deterioration beyond two months from the clinical onset.

Statistical analysis

Analysis of lifestyle and dietary habits as risk factors for CIDP was performed using multivariable logistic regression models with the case or control status as dependent variable and each lifestyle and dietary habit variable, separately, as predictor. Given the different sex distribution between patients and controls (males were 66% of the total in the patients group and 32% of the total in the controls group), a gender-matched analysis was performed with randomly-selected controls to obtain a 1:1 ratio between patients and controls. For the analysis on risk factors for CIDP the probability modeled is that of being a case. All tests were two-tailed and the significance level was set at 5%. Analyses were carried out using the SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Lifestyle and dietary factors associated with CIDP risk

A total of 323 patients (109 females; 214 males) with a diagnosis of CIDP according to the EFNS/PNS criteria completed the study on lifestyle and dietary habits. The mean disease duration at study entry was 8.5 years (SD 8.3 years). Dietary and lifestyle data were collected from 266 controls (180 females; 86 males). A total of 195 cases and 195 randomly sex–matched controls were used for the analysis (109 females; 86 males).

A reduced risk of CIDP was found in those who eat rice ≥3 times per week (OR= 0.42, 95% CI = 0.20–0.87) (table 2). Fish intake of at least once per week was associated with a reduced risk of CIDP (OR= 0.53, 95% CI = 0.34–0.83) (table 2). None of the remaining examined variables in table 2 revealed significant associations.

Antecedent events and infections

Data on antecedent events were available from 411 patients with CIDP (147 females; 264 males, with a mean disease duration at entry of 8 years [SD 8]). Thirty-two (8%) patients had a flu-like syndrome within 1-42 days before the onset of CIDP symptoms, 9 (2%) had an upper respiratory infection, 9 (2%) a gastrointestinal infection, 7 (1.5%) had vaccination (all seven with flu vaccine), 4 (1%) had surgery, and 2 (0.5%) had trauma. No patients started a new immune-modulating therapy (table 3). Overall, 63 (15.5%) had an antecedent event in the 1 through 42 days prior to CIDP onset with a mean time between the antecedent event and symptoms onset of 16.5 days (1-40 days). Fifty (12%) patients reported an antecedent infection occurred on average 17 days (1-40 days) before symptoms onset. Patients with an antecedent infection more frequently had an A-CIDP onset (26% vs 8%; p= 0.0004) and

cranial nerve involvement (42% vs 18%; p= 0.0050) than patients without an antecedent infection (table 4). No other differences were found between the two groups.

Discussion

In this study, we found that some dietary habits, including eating rice at least three times per week and eating fish at least once per week, are associated with a decreased risk of CIDP.

Rice-derived bioactive compounds have been demonstrated to have antioxidant and anti-inflammatory potential in various ex-vivo[22,23] and animal models[23-24]. Pigmented rice demonstrated to have higher antioxidant and anti-inflammatory capacity compared to non-pigmented rice[25], which is the most consumed rice variety in Italy. However, even after the refining process, white rice still contains antioxidant nutrients[26]. Little is known however on the possible immunomodulatory activity of white rice. Fish-derived bioactive compounds showed remarkable anti-inflammatory and immune-modulatory activities[27,28], and fish consumption was associated with a decreased risk of autoimmune diseases including MS[29,30], asthma[31], and RA[32,33]. Whether this may also explain the reduced prevalence of CIDP in Japan (1.61/100.000)[13], where the traditional diet is characterized by high consumption of rice and fish, compared to Europe and United States (range 3 to 8.9/100.000)[11,17] remains unclear.

We found a similarly frequency of antecedent events and, more specifically, of antecedent infections or vaccinations in our patients with CIDP compared to what observed in previous studies (Table 1)[5-12]. Even if our study did not include a control group for comparison, the frequency of antecedent infections or vaccinations was similar to what previously observed in the controls of a case-control study on Italian GBS patients (13.5% vs 23.7%)[34] and was

consistently lower than reported in studies on GBS patients[34,35]. Therefore, our study seems to suggest that antecedent events are unlikely to play a role in the risk of CIDP. There are few data on the associations of infections with the clinical features of CIDP. A similar prevalence of preceding infections was found between A-CIDP and chronic CIDP in a small number of patients[7]. Patients with A-CIDP had a similar frequency of preceding infections than patients with GBS with treatment-related fluctuations[36]. In our study, antecedent infections were associated with an acute onset of CIDP and with cranial nerve involvement, suggesting that CIDP patients with these antecedent events might share some clinical features with GBS.

Limitations of our study include the use of a non-validated questionnaire and the selection of patient's partners as controls. This selection bias was however attenuated by matching for sex and by randomly choosing controls for the analysis. Another limitation of the study derives from the long disease duration with a consequent risk of recall bias. We tried to reduce this risk by including only the patients who reported not having changed their diet and the lifestyle habits investigated in the study after the onset of the disease, even if the absence of previous data on the possible role of diet, smoking and alcohol consumption in CIDP makes it unlikely that patients had changed their lifestyle habits. It is also possible that the increased frequency of antecedent infections in patients with A-CIDP is due to recall bias as these events can be more easily linked with an acute onset of CIDP. However, the presence of a more frequent cranial nerve involvement in this group makes it unlikely that our findings can be fully explained by recall or selection bias. The absence of a control group for the analysis of antecedent events is another major limitation of this study. However, the low frequency of antecedent events reported and the results of studies in other populations suggest that a role of antecedent events in CIDP risk is unlikely. More epidemiological and intervention studies

are necessary to investigate in more detail the role of environmental factors in the risk of CIDP.

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Conflict of interest, acknowledgement, funding and contributions of authors statements are included as 'supplementary material'.

Table legends

Table 1. Reported frequency of antecedent events in CIDP

Table 2. Frequency of lifestyle and dietary habits exposure in patients with CIDP and controls

*Main exposure significant at $p < 0.05$. Analysis was not performed if one cell contained fewer than 10 individuals.

CI = confidence interval; NA = not available; OR = odds ratio;

Table 3. Type of antecedent event in 411 patients with CIDP

Table 4. Comparison of clinical features and treatment response in CIDP patients with and without an antecedent infection

* statistically significant (p value < 0.05).

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy ; F = female; GBS: Guillain-Barré syndrome; INCAT = Inflammatory Neuropathy Cause and Treatment ; IVIg = intravenous immunoglobulin; M = male

Table 1. Reported frequency of antecedent events in CIDP

Authors and year of publication	Number of patients analysed	Frequency of antecedent events (%)	Frequency of infection or vaccination (%)
Oh SJ et al., 1978 [5]	10	2 (20%)	2 (20%)
Oh SJ et al., 1978 [5] (literature review)	54		14 (26%)
Dyck PJ and Arnason B, 1984 [6]	57	10 (19%)	3 (5%)
McCombe PA et al., 1987 [7]	92	29 (32%)	29 (32%)
Simmons Z et al., 1993 [8]	103	25 (24%)	20 (19%)
Simmons Z et al., 1997 [9]	children: 15 adults: 69	children: 5 (33%) adults: 17 (25%)	children: 4 (27%) adults: 12 (17%)
Gorson KC et al., 1997 [10]	67	14 (21%)	12 (18%)
Chiò A et al., 2007 [11]	294	15 (9.7%)	15 (9.7%)
Kuitwaard K et al., 2009 [12]	76		8 (11%) vaccination

Table 2. Frequency of lifestyle and dietary habits exposure in patients with CIDP and controls

	Cases		Controls		OR	95% CI	p value
	N	%	N	%			
Exposure to toxic agents							0.0750
Never or occasional	167	85.6	176	91.2	1 (ref.)		
Prolonged	28	14.4	17	8.8	1.85	0.94-3.63	
NA	0		2				
Smoke							0.1056
No	117	60.0	130	67.4	1 (ref.)		
Yes	78	40.0	63	32.6	1.43	0.93-2.20	
NA	0		2				
Alcohol consumption							0.2999
No	139	71.3	129	66.8	1 (ref.)		
Yes	56	28.7	64	33.2	0.79	0.50-1.24	
NA	0		2				
Illicit drugs consumption							0.6569
Never or occasional	185	98.4	180	97.8	1 (ref.)		
Repeated	3	1.6	4	2.2	0.67	0.11-3.99	
NA	7		11				
Dietary regimen							0.9999
Omnivorous	192	98.5	183	97.3	1 (ref.)		
Other	0	0.0	2	1.1	-	-	
Vegetarian	3	1.5	3	1.6	1.00	0.20-4.96	
NA	0		7				
Pasta							0.0803
≤2 times per week	63	32.5	44	22.6	1 (ref.)		
3-4 times per week	73	37.6	88	45.1	0.56	0.34-0.94	
≥5 times per week	58	29.9	63	32.3	0.63	0.36-1.08	
NA	1		0				
Rice							0.0408*
<1 time per week	59	30.4	54	27.7	1 (ref.)		
1-2 times per week	117	60.3	106	54.4	0.95	0.60-1.50	
≥3 times per week	18	9.3	35	17.9	0.42	0.20-0.87*	
NA	1		0				
Meat							0.6490
<1 time per week	20	10.3	15	7.7	1 (ref.)		
1-2 times per week	86	44.3	88	45.1	0.74	0.36-1.52	

≥3 times per week	88	45.4	92	47.2	0.70	0.32-1.50	
NA	1		0				
Raw meat							0.3070
Never	99	51.0	113	58.0	1 (ref.)		
<1 time per week	42	21.7	33	16.9	1.53	0.87-2.68	
≥1 time per week	53	27.3	49	25.1	1.29	0.78-2.13	
NA	1		0				
White meat							0.4106
<1 time per week	34	17.5	25	12.8	1 (ref.)		
1-2 times per week	108	55.7	117	60.0	0.67	0.36-1.21	
≥3 times per week	52	26.8	53	27.2	0.68	0.34-1.36	
NA	1		0				
Fish							0.0053*
<1 time per week	73	37.6	47	24.4	1 (ref.)		
≥1 time per week	121	62.4	146	75.6	0.53	0.34-0.83	
NA	1		2				
Vegetables							0.7500
≤2 times per week	27	13.9	26	13.3	1 (ref.)		
3-4 times per week	48	24.7	42	21.5	1.09	0.54-2.24	
≥5 times per week	119	61.3	127	65.1	0.92	0.49-1.71	
NA	1		0				
Fruits							0.5056
≤2 times per week	30	15.5	30	15.4	1 (ref.)		
3-4 times per week	30	15.5	22	11.3	1.33	0.61-2.86	
≥5 times per week	134	69.0	143	73.3	0.94	0.51-1.73	
NA	1		0				
Cheese							0.5158
<1 time per week	42	21.6	37	19.1	1 (ref.)		
1-2 times per week	70	36.1	64	33.0	1.01	0.58-1.76	
≥3 times per week	82	42.3	93	47.9	0.79	0.46-1.35	
NA	1		1				
Eggs							0.7226
<1 time per week	64	33.2	64	32.8	1 (ref.)		
1-2 times per week	114	59.1	120	61.5	0.96	0.63-1.46	
≥3 times per week	15	7.8	11	5.6	1.33	0.59-3.00	
NA	2		0				
Sweets							0.6685
<1 time per week	57	29.4	56	28.7	1 (ref.)		

1-2 times per week	64	33.0	72	36.9	0.85	0.51-1.41	
≥3 times per week	73	37.6	67	34.4	1.06	0.65-1.73	
NA	1		0				
Coffee							0.2995
Never	28	14.4	23	11.9	1 (ref.)		
≤4 times per week	26	13.4	18	9.3	1.24	0.52-2.96	
≥5 times per week	140	72.2	152	78.8	0.76	0.40-1.45	
NA	1		2				
Tea							0.2669
Never	85	43.8	100	51.3	1 (ref.)		
≤2 times per week	58	29.9	45	23.1	1.49	0.92-2.42	
≥3 times per week	51	26.3	50	25.6	1.23	0.73-2.06	
NA	1		0				
Milk							0.0944
Never	68	35.2	88	45.1	1 (ref.)		
≤4 times per week	47	24.4	44	22.6	1.43	0.85-2.41	
≥5 times per week	78	40.4	63	32.3	1.69	1.04-2.74	
NA	2		0				
Soft drinks							0.3294
Never	106	54.6	120	61.9	1 (ref.)		
≤2 times per week	55	28.4	50	25.8	1.18	0.76-1.83	
≥3 times per week	33	17.0	24	12.4	1.54	0.85-2.80	
NA	1		1				

*Main exposure significant at $p < 0.05$. Analysis was not performed if one cell contained fewer than 10 individuals.

CI = confidence interval; NA = not available; OR = odds ratio;

Table 3. Type of antecedent event in 411 patients with CIDP

Antecedent events	**Number of patients (%)**
Flu-like syndrome	32 (8%)
Upper respiratory infection	9 (2%)
Gastrointestinal infection	9 (2%)
Vaccination	7 (1.5%)
Surgery	4 (1%)
Trauma	2 (0.5%)
Therapy before disease onset	none

Table 4. Comparison of clinical features and treatment response in CIDP patients with and without an antecedent infection

	CIDP patients with an antecedent infection (n. 50)	**CIDP patients without an antecedent infection (n. 361)**	**p value**
Age at onset; years; mean (range)	48 (18-82)	50 (6-82)	0.3251
Disease duration; years; mean (range)	7 (0.5-38)	8 (0.5-52)	0.1798
Gender (M:F)	28:22	240:121	0.1558
Acute clinical onset	13 (26%)	28 (8%)	0.0004*
Autonomic symptoms	4 (8%)	25 (7%)	1.0000
Cranial nerve involvement	21 (42%)	65 (18%)	0.0050*
Pain	17 (34%)	111 (31%)	0.6286
Ataxia	18 (36%)	105 (29%)	0.3258
INCAT disability score; mean (range)	3 (0-10)	2.5 (0-10)	0.2343
Response to steroids	14/33 (55%)	104/200 (51%)	0.3503
Response to IVIg	35/47 (74%)	195/266 (73%)	1.0000

* statistically significant (p value < 0.05).

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy ; F = female; INCAT = Inflammatory Neuropathy Cause and Treatment ; IVIg = intravenous immunoglobulin; M = male