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

Pietro E. Doneddu,[1] Elisa Bianchi,[2] Dario Cocito,[3] Fiore Manganelli,[4] Raffaella Fazio,[5] Massimiliano Filosto,[6] Anna Mazzeo,[7] Giuseppe Cosentino,[8] Andrea Cortese,[9] Stefano Jann,[10] Angelo M. Clerici,[11] Giovanni Antonini,[12] Gabriele Siciliano,[13] Marco Luigetti,[14] Girolama A. Marfia,[15] Chiara Briani,[16] Giuseppe Lauria,[17] Tiziana Rosso,[18] Guido Cavaletti,[19] Marinella Carpo,[20] Luana Benedetti,[21] Ettore Beghi,[2] Giuseppe Liberatore,[1] Lucio Santoro,[4] Erdita Peci,[3] Stefano Tronci,[5] Stefano Cotti Piccinelli,[6] Antonio Toscano,[7] Laura Piccolo,[9] Elena P. Verrengia,[10] Luca Leonardi,[12] Erika Schirinzi,[13] Giorgia Mataluni,[15] Marta Ruiz,[16] Patrizia Dacci,[17] Eduardo Nobile-Orazio[1] on behalf of the Italian CIDP Database Study Group.

1. Milan University, Humanitas Clinical and Research Institute, Rozzano, Milan, Italy
2. Laboratorio di Malattie Neurologiche, Istituto Mario Negri IRCCS, Milan, Italy
3. Department of Neuroscience, University of Turin, Turin, Italy
4. University of Naples 'Federico II', Naples, Italy
5. San Raffaele Scientific Institute, Milan, Italy
6. ASST ‘Spedali Civili’, University of Brescia, Brescia, Italy
7. University of Messina, Messina, Italy
8. University of Palermo, Palermo, Italy
9. IRCCS Foundation C. Mondino, Pavia, Italy
10. Niguarda Ca' Granda Hospital, Milan, Italy
11. Neurology Unit, Circolo & Macchi Foundation Hospital, Varese, Italy
12. 'Sapienza' University of Rome, Sant'Andrea Hospital, Rome, Italy
13. University of Pisa, Pisa, Italy
14. Catholic University of Sacred Heart, Rome, Italy
15. Tor Vergata University of Rome, Rome, Italy
16. University of Padua, Padua, Italy
17. IRCCS Foundation ‘Carlo Besta’, University of Milan, Milan, Italy
18. UOC Neurologia-Castelfranco Veneto, Treviso, Italy
19. University of Milano-Bicocca, Monza, Italy
20. ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy
21. Sant'Andrea Hospital, La Spezia, Italy

Address Correspondence to: Eduardo Nobile-Orazio, MD, PhD, FAAN, Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, Milan 20089, Italy. Tel: +390282242209; Fax: +390282242298; E-mail: eduardo.nobile@unimi.it

Word count: 3755
Running title: risk factors in CIDP
Key words: Chronic inflammatory demyelinating neuropathy; CIDP; Epidemiology; Diet; Lifestyle, Infections; Vaccination

Conflicting interests

DC received honoraria for lecturing from Shire, CSL Behring, and Kedrion. CB served on scientific advisory boards for Pfizer. EB received grants from UCB-Pharma, Shire, Italian Ministry of Health, Fondazione Borgonovo, and Associazione IDIC 15. LS and FM received personal fees for scientific events from CSL Behring. GC has received honoraria for lecturing from Kedrion. MF has served on scientific advisory boards for CSL Behring. SJ has received research grants from Grifols. ENO reports consultation fees from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, Astellas, the Netherlands. ENO, DC, EP, PED, GL, EP, RF, MC, AM, CB, GC, BF, AC, LS, FM, GC, MF, SJ has received travel grants from CSL Behring or Kedrion or both. The other authors declare no conflict of interest.

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 nerve disorder 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 possibly by favoring immune-mediated pathogenesis. 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 or one of its variants [18] according to the EFNS/PNS[19] criteria were included. At enrollment all eligible patients underwent a detailed clinical history (including time of onset of symptoms), timing and distribution of neurological signs, and a number of disability scales. We used a structured questionnaire to explore the prevalence of some lifestyle and dietary habits in patients with CIDP. Only patients who reported not to have changed their diet or the lifestyle habits 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 were highly unbalanced by sex, we opted for a 1:1 sex-matching of patients with randomly-selected controls.

We also collected information on the occurrence of antecedent events within six weeks[21-22] before the onset of symptoms using as reference data from previous studies in Italy. We also analyzed whether patients with antecedents infections had different clinical characteristics than those without these antecedent.

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 within 6 weeks before the onset of symptoms 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.

Statistical analysis

Descriptive statistics were reported as count and percentage for categorical variables and mean, standard deviation (SD), median, interquartile range (IQR) or range for continuous variables. 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 female and 214 male) with a diagnosis of CIDP according to the EFNS/PNS criteria completed the study on lifestyle and dietary habits.. Dietary and lifestyle data were collected from 266 controls (180 females and 86 males). A total of 195 cases and 195 randomly sex–matched controls were used for the analysis (109 females and 86 males).

Table 2 shows the odds ratios (ORs) for each of the lifestyle and dietary factors. 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). 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). 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 (264 men and 147 women with a mean age at entry of 58 years [SD 15.3] and a disease duration of 8 years [SD 8]). Thirty-two

(8%) patients had a flu-like syndrome within six weeks 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 prior to CIDP onset with a mean time between the antecedent event and symptoms onset of 16.5 days (1-40 days). The clinical features and treatment response of the 50 (12%) patients with CIDP who reported an infection 1-40 days (mean 17 days) before CIDP are summarized in table 4. They had 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.

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[23-27] and animal models[26-28]. Pigmented rice demonstrated to have higher antioxidant and anti-inflammatory capacity compared to non-pigmented rice[26,29], which is the most consumed rice variety in Italy. However, even after the refining process, white rice still contains antioxidant nutrients[30]. Little is known on the possible immunomodulatory activity of white rice. Fish-derived bioactive compounds showed remarkable anti-inflammatory and immune-modulatory activities[31-33], and fish consumption was associated with a decreased risk of autoimmune diseases including MS[34-37], asthma[38], and RA[39,40]. Whether this may also explain the reduced prevalence of CIDP in Japan (1.61/100.000)[14], 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)[12,18] 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)[6-13]. 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%)[41] and was consistently lower than reported in studies on GBS patients[41,42]. There are few data on the association of infections with the clinical features of CIDP. A similar prevalence of preceding infections was found in patients with an acute or not acute onset of CIDP[8]. Patients with A-CIDP had a similar frequency of preceding infections that patients with GBS with treatment-related fluctuations[43] but were less common than in GBS[44]. 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 compensate this by including only the patients who reported not to have changed their diet and the lifestyle habits 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 change their lifestyle habits. It is also possible that the increased frequency of antecedent infections in patients with A-CIDP might be due to recall bias as these events can be more easily linked with an acute onset but might not justify the more frequent cranial nerve involvement in this group of patients. The absence of a control group for the analysis of antecedent events is also a major limitation of this study even if the comparison with studies with the patients and controls from other populations suggests that a role of antecedent events in CIDP risk is unlikely. More epidemiological and intervention studies are however necessary to investigate in more detail the role of environmental factors in the risk of CIDP.

References

1. Nobile-Orazio E. Chronic Inflammatory demyelinating polyradiculoneuropathy. Where we are, where we should go. *Journal of the Peripheral Nervous System* 2014; **19**(1): 2-13.
2. Jelinek GA, De Livera AM, Marck CH, et al. Associations of Lifestyle, Medication, and Socio-Demographic Factors with Disability in People with Multiple Sclerosis: An International Cross-Sectional Study. *PLoS One* 2016; 25; 11(8):e0161701.
3. Belbasis L, Bellou V, Evangelou E, Ioannidis JPA, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *The Lancet Neurology* 2015; **14**(3): 263-273.
4. Manzel A, Muller DN, Hafler DA, Erdman SE, Linker RA, Kleinewietfeld M. Role of "Western Diet" in Inflammatory Autoimmune Diseases. *Current allergy and asthma reports* 2014; **14**(1): 404.
5. Oh SJ. Subacute demyelinating polyneuropathy responding to corticosteroid treatment. *Archives of neurology* 1978; **35**(8): 509-516.
6. Dyck PJ, Arnason B. Chronic inflammatory demyelinating polyradiculoneuropathy. In: *Peripheral Neuropathy, Volume 2*. Edited by P.J. Dyck, P.K. Thomas, E.H. Lambert and R. Bunge. Philadelphia and London: W.B. Saunders, 1984: 2101-2114.
7. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. *Brain* 1987; **110**(6): 1617-1630.
8. Simmons Z, Albers JW, Bromberg MB, Feldman EL. Presentation and initial clinical course in patients with chronic inflammatory demyelinating polyradiculoneuropathy: comparison of patients without and with monoclonal gammopathy. *Neurology* 1993; **43**(11): 2202-2209.

9. Simmons Z, Wald JJ, Albers JW. Chronic inflammatory demyelinating polyradiculoneuropathy in children: I. Presentation, electrodiagnostic studies, and initial clinical course, with comparison to adults. *Muscle Nerve* 1997; **20**(8):1008-1015.
10. Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. *Neurology* 1997; **48**(2):321-328.
11. Chio` A, Cocito D, Bottacchi E, et al; The PARCIDP. Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *Journal of Neurology, Neurosurgery, and Psychiatry* 2007; **78**(12): 1349–1353.
12. Kuitwaard K, Bos-Eyssen ME, Blomkwist-Markens PH, van Doorn PA. Recurrences, vaccinations and long-term symptoms in GBS and CIDP. *Journal of the Peripheral Nervous System* 2009; **14**(4): 310-315.
13. Iijima M, Koike H, Hattori N, et al.; Refractory Peripheral Neuropathy Study Group of Japan. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. *Journal of Neurology, Neurosurgery, and Psychiatry* 2008; **79**(9): 1040-1043.
14. Lefter S, Hardiman O, Ryan AM. A population-based epidemiologic study of adult neuromuscular disease in the Republic of Ireland. *Neurology* 2017; **88**(3): 304-313.
15. Mahdi-Rogers M, Hughes RA. Epidemiology of chronic inflammatory neuropathies in southeast England. *European Journal of Neurology* 2014; **21**(1): 28-33.
16. McLeod JC, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. *Annals of Neurology* 1999; **46**(6): 910–913.
17. Laughlin RS, Dyck PJ, Melton LJ 3rd, Leibson C, Ransom J, Dyck PJ. Incidence and prevalence of CIDP and the associations with diabetes mellitus. Neurology 2009; **73**(1): 39–45.

18. Doneddu PE, Cocito D, Manganelli F, et al.; Italian CIDP Database study group. Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP Database. *Journal of Neurology, Neurosurgery, and Psychiatry* 2018; Oct 8. pii: jnnp-2018-318714. doi: 10.1136/jnnp-2018-318714. [Epub ahead of print]
19. Joint Task Force of the EFNS and the PNS. 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. *Journal of the Peripheral Nervous System* 2010; **15**(1): 1-9.
20. Greene SK, Rett MD, Vellozzi C, et al. Guillain-Barré Syndrome, Influenza Vaccination, and Antecedent Respiratory and Gastrointestinal Infections: A Case-Centered Analysis in the Vaccine Safety Datalink, 2009-2011. *PLoS One* 2013; **8**(6): e67185.
21. Tokars JI, Lewis P, DeStefano F, et al. The risk of Guillain-Barré syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: results from self-controlled analyses. *Pharmacoepidemiol Drug Saf* 2012; **21**(5): 546-552.
22. Callcott ET, Blanchard CL, Oli P, Santhakumar AB. Pigmented Rice-derived Phenolic Compounds Reduce Biomarkers of Oxidative Stress and Inflammation in Human Umbilical Vein Endothelial Cells. *Molecular Nutrition & Food Research* 2018; Dec;62(24):e1800840. doi: 10.1002/mnfr.201800840. Epub 2018 Nov 22.
23. Shen J, Yang T, Xu Y, et al. δ-Tocotrienol, Isolated from Rice Bran, Exerts an Anti-Inflammatory Effect via MAPKs and PPARs Signaling Pathways in Lipopolysaccharide-Stimulated Macrophages. *International Journal of Molecular Sciences* 2018; Oct 4;19(10). pii: E3022.
24. Callcott ET, Thompson K, Oli P, Blanchard CL, Santhakumar AB. Coloured rice-derived polyphenols reduce lipid peroxidation and pro-inflammatory cytokines ex vivo. *Food & Function* 2018; Oct 17;9(10):5169-5175.

25. Dias ALS, Pachikian B, Larondelle Y, Quetin-Leclercq J. Recent advances on bioactivities of black rice. *Current Opinion in Clinical Nutrition & Metabolic Care* 2017; **20**(6): 470-476.
26. Kurtys E, Eisel ULM, Hageman RJJ, et al. Anti-inflammatory effects of rice bran components. *Nutrition Reviews* 2018; **76**(5): 372-379.
27. Zhao L, Zhang Y, Liu G, Hao S, Wang C, Wang Y. Black rice anthocyanin-rich extract and rosmarinic acid, alone and in combination, protect against DSS-induced colitis in mice. Food & Function 2018; **9**(5): 2796-2808.
28. Okonogi S, Kaewpinta A, Junmahasathien T, Yotsawimonwat S. Effect of rice variety and modification on antioxidant and anti-inflammatory activities. *Drug Discoveries & Therapeutics* 2018; **12**(4): 206-213.
29. Patil SB, Khan MK. Germinated brown rice as a value added rice product: A review. *Journal of Food Science and Technology* 2011; **48**(6): 661–667.
30. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. *American Journal of Clinical Nutrition* 2006; 83(6 Suppl):1505S-1519S. doi: 10.1093/ajcn/83.6.1505S.
31. Liuzzi GM, Latronico T, Rossano R, Viggiani S, Fasano A, Riccio P. Inhibitory effect of polyunsaturated fatty acids on MMP-9 release from microglial cells-implications for complementary multiple sclerosis treatment. *Neurochemical Research* 2007; **32**(12): 2184–2193.
32. Kelley DS. Modulation of human immune and inflammatory responses by dietary fatty acids. *Nutrition* 2001; **17**(7-8): 669-673.
33. Swank RL, Lerstad O, Strom P, Barker J. Multiple sclerosis in rural Norway; its geographic and occupational incidence in relation to nutrition. *New England Journal of Medicine* 1952; **246**(19): 721-728.
34. Agranoff BW, Goldberg D. Diet and the geographical distribution of multiple sclerosis. *Lancet* 1974; **2**(7888): 1061-1066.
35. Bäärnhielm M, Olsson T, Alfredsson L. Fatty fish intake is associated with decreased occurrence of multiple sclerosis. *Multiple Sclerosis* 2014; **20**(6): 726-732.

36. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, Kaufman JS. Estimating the Marginal Causal Effect of Fish Consumption during Adolescence on Multiple Sclerosis: A Population-Based Incident Case-Control Study. *Neuroepidemiology* 2018; **50**(3-4): 111-118.
37. Papamichael MM, Shrestha SK, Itsiopoulos C, Erbas B. The role of fish intake on asthma in children: A meta-analysis of observational studies. *Pediatric Allergy and Immunology* 2018; **29**(4): 350-360.
38. Di Giuseppe D, Wallin A, Bottai M, Askling J, Wolk A. Long-term intake of dietary long-chain n-3 polyunsaturated fatty acids and risk of rheumatoid arthritis: a prospective cohort study of women. *Annals of the Rheumatic Diseases* 2014; **73**(11): 1949-1953.
39. Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M, Nelson JL. Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. *Epidemiology* 1996; **7**(3): 256-263.
40. Galeotti F, Massari M, D'Alessandro R, et al.; ITANG study group. Risk of Guillain-Barré syndrome after 2010-2011 influenza vaccination. *Eur J Epidemiol* 2013; **28**(5): 433-444.
41. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. *Neuroepidemiology* 2009; **32**(2): 150-163.
42. Ruts L, Drenthen J, Jacobs BC, et al. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. *Neurology* 2010; **74**(21): 1680-1686.
43. Dionne A, Nicolle MW, Hahn AF. Clinical and electrophysiological parameters distinguishing acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2010; **41**(2): 202-207.

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 ;

Contributors

PED contributed to the conception of the research project, reviewed and commented on the statistical analysis, wrote the first draft of the report, and reviewed the report. DC, FM, RF, MF, AM, GC, AC, SJ, AMC, GA, GS, ML, GAM, CB, GL, TR, GC, MC, LB, EB, GL, LS, EP, ST, SCP, AT, LP, EPV, LL, ES, GM, MR, PD contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. EB designed and executed the statistical analysis, contributed to the conception, organization, and execution of the research project, reviewed and commented on the statistical analysis and the report. ENO conceived, organized and designed the study, reviewed and commented on the statistical analysis, wrote the first draft of the report, reviewed the report.

Funding

The study was supported by a Grant from Regione Lombardia, Italy, for patients from this Region and subsequently extended to other Italian Centers. The study was also supported by unrestricted grants from Kedrion Biopharma (Italy), CSL Behring (Italy), Humanitas Clinical and Research Institute (Milan, Italy), and GBS-CIDP Foundation International (USA). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

Pietro Emiliano Doneddu, Giuseppe Liberatore, Francesca Gallia, and Eduardo Nobile-Orazio from the Department of Medical Biotechnology and Translational Medicine, Neuromuscular and Neuroimmunology Service, Humanitas Clinical and Research Institute, Milan University, Rozzano, Milan, Italy; Erdita Peci and Dario Cocito from the Department of Neuroscience, University of Turin, Turin, Italy. Daniele Velardo, Stefano Tronci and Raffaella Fazio from the Division of Neuroscience, Department of Neurology, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan, Italy; Fiore Manganelli and Lucio Santoro from the Department of Neuroscience, Reproductive Sciences and Odontostomatology, University of Naples 'Federico II', Naples, Italy; Marta Ruiz and Chiara Briani from the Neurology Unit, Department of Neuroscience, University of Padua, Padua, Italy. Stefano Cotti Piccinelli, Alice Todeschini and Massimiliano Filosto from the Center for Neuromuscular Diseases and Neuropathies, Unit of Neurology ASST 'Spedali Civili', University of Brescia, Brescia, Italy; Alessandro Beronio and Luana Benedetti from the Neurology Unit, Sant'Andrea Hospital, La Spezia, Italy; Antonio Toscano, Luca Gentile and Anna Mazzeo from the Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina, Italy; Giorgia Mataluni and Girolama Alessandra Marfia from the Disimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; Laura Piccolo, Ilaria Callegari and Andrea Cortese from the IRCCS Foundation C. Mondino National Neurological Institute, Pavia, Italy; Giuseppe Cosentino and Brigida Fierro from the Department of Experimental BioMedicine and Clinical Neurosciences (BioNeC), University of Palermo, Palermo, Italy; Verrengia Elena Pinuccia and Stefano Jann from the Department of Neuroscience, Niguarda Ca' Granda Hospital, Milan, Italy; Elisa Bianchi and Ettore Beghi from the Laboratorio di Malattie Neurologiche, IRCCS-Istituto Mario Negri, Milan, Italy; Angelo Maurizio Clerici from the Neurology Unit, Circolo & Macchi Foundation Hospital, Insubria University, DBSV, Varese, Italy; Federica Scrascia and Marinella Carpo from the ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy; Martina Garnero and Angelo Schenone from the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy; Marco Luigetti and Mario Sabatelli from the Department of Neurology, Catholic University of Sacred Heart, Rome, Italy; Patrizia Dacci and Giuseppe Lauria from the Unit of Neuroalgology, IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy; Luca Leonardi and Giovanni Antonini from the Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, 'Sapienza' University of Rome, Sant'Andrea Hospital, Rome, Italy; Tiziana Rosso from the Azienda UL.SS. 8 Asolo, Castelfranco Veneto, Italy; Erika Schirinzi and Gabriele Siciliano from the Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; Claudia Balducci and Guido Cavaletti from the School of Medicine and Surgery and Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy.

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 [6]	10	2 (20%)	2 (20%)
Oh SJ et al., 1978 [6] (literature review)	54		14 (26%)
Dyck PJ and Arnason B, 1984 [7]	57	10 (19%)	3 (5%)
McCombe PA et al., 1987 [8]	92	29 (32%)	29 (32%)
Simmons Z et al., 1993 [9]	103	25 (24%)	20 (19%)
Simmons Z et al., 1997 [10]	children: 15 adults: 69	children: 5 (33%) adults: 17 (25%)	children: 4 (27%) adults: 12 (17%)
Gorson KC et al., 1997 [11]	67	14 (21%)	12 (18%)
Chiò A et al., 2007 [12]	294	15 (9.7%)	15 (9.7%)
Kuitwaard K et al., 2009 [13]	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							0.0163*
<1 time per week	73	37.6	47	24.4	1 (ref.)		
1-2 times per week	94	48.5	118	61.1	0.50	0.31-0.80*	
≥3 times per week	27	13.9	28	14.5	0.63	0.33-1.20	
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 ;