

Impact of environmental factors and physical activity on disability and quality of life in CIDP.

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Abstract

A few observational studies and randomized trials suggest that exercise and rehabilitation may improve activity limitation and quality of life (QoL) in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but the impact of other modifiable factors on the severity of the disease is not well understood. Using a structured questionnaire we collected data on lifestyle and dietary habits of the patients included in the Italian CIDP database to investigate the possible influence of modifiable lifestyle factors ~~in the progression of~~ on disability and QoL. Questionnaire data were available for 323 patients. The effect of lifestyle and dietary exposures on impairment, disability and QoL was evaluated using logistic regression models, adjusting for age, sex, disease duration, physical activity and smoke. Physical activity was associated with lower sensory impairment by the ISS scale, less disability by the INCAT and RODS scale and a better QoL in all the domains of EURO-QoL scale with the exception of **anxiety/depression**. None of the other parameters had an impact on these scales. This study adds evidence to the possible role of physical activity in improving symptoms severity, disability and QoL in patients with CIDP. None of the other environmental factors investigated appeared to have an impact on the severity and health perception of CIDP.

Key words

Chronic inflammatory demyelinating polyradiculoneuropathy; CIDP; Physical activity; Epidemiology; Disability; Quality of life

Declaration

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Availability of data and material

The data that support the findings of this study are available from the corresponding author, upon request.

Authors' contributions

PED design and conceptualized study, major role in acquisition of data, analyzed the data, and wrote the first draft of the manuscript. EBianchi 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. DC, FM, RF, MF, EBeghi, AM, GC, AC, SJ, AMC, GA, GS, GAM, CB, GL, TR, GC, MC, LB, AS, GL, EP, ES, ST, SCP, AT, LG, LP, EPV, LL, ES, GM, MR, MS, LS contributed to the study conception and design, major role in acquisition and interpretation of data, revised the manuscript for intellectual content. ENO conceived, organized and designed the study, reviewed and commented on the statistical analysis, reviewed the report.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated chronic neuropathy leading to a temporary or permanent disability in about 50% of the patients [1]. Several retrospective studies on large series of patients and a few randomized controlled trials have shown the efficacy of corticosteroids, plasma exchange, and intravenous immunoglobulin (IVIg) in CIDP [1]. However, only about 80% of patients respond to these therapies [1]. A possible influence of modifiable lifestyle components on the progression of the disease has been reported in other immune-mediated diseases including multiple sclerosis and rheumatoid arthritis [2-11]. A possible role of physical activity or rehabilitation in reducing disability has been reported in patients with inflammatory neuropathies [12-21] (Table 1), while the contribution of other potentially modifiable factors has not been investigated. The identification of these modifiable environmental factors might form the basis of a secondary preventive approach to disease management. **Recently, we found that consumption of rice and fish were associated with lower risk to develop CIDP.** [22]. We now investigated the association of some lifestyle and dietary habits with disability, symptom severity and QoL in patients with CIDP.

Materials and Methods

Study design

We implemented a web-based database on Italian CIDP patients where, at present, data from 500 patients with a diagnosis of CIDP or one of its variants, followed by 22 Italian Centers with expertise in immune-mediated neuropathies, are included [23]. At enrolment, all eligible patients underwent a detailed clinical history including timing and distribution of neurological signs, a number of disability scales, and a QoL scale. We used the same methodology as the one employed in a previous study [23]. In this study, we collected information about lifestyle and dietary habits, **related to the period after CIDP diagnosis,** using a structured questionnaire. Inclusion criteria for this study were patients fulfilling the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) diagnostic criteria for CIDP [24]. Patients with a clinical diagnosis of

CIDP not fulfilling the EFNS/PNS criteria were excluded, as were patients with an alternative diagnosis for the neuropathy or with increased titers of anti-MAG (myelin-associated glycoprotein) antibodies (over 7000 by Bühlman method) or without available nerve conduction studies. **Only the patients with an IgM monoclonal gammopathy were tested for anti-MAG antibodies.** All the data were included by the treating neurologist in a web-based electronic database expressly prepared by CINECA, Bologna, Italy.

Assessment of lifestyle and dietary habits

We asked the patients for exposure to toxic agents (prolonged vs. never/occasionally), smoking (including duration and amount of exposure), illicit drugs consumption (repeated vs. never/occasionally), **regular alcohol use including amount of exposure (1-3 drinks per day, 4-6 drinks per day, 7-9 drinks per day, \geq 10 drinks per day on average)**, regular physical activity (type [walking for at least 30 minutes, running, swimming, cycling, gymnastic, team sport, others to be specified] and frequency [$<$ 1 time per week, 1 time per week, 2-3 times per week, $>$ 3 times per week]), 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 impairment, disability, and quality of life

The clinical evaluation at enrollment included the following outcome measures: muscle strength measured by the Medical Research Council (MRC) sumscore on 12 muscles (range from 0-worst to 60-best); overall sensory function measured by the INCAT sensory scale (ISS) (range from 0-best to 20-worst); neurological disability evaluated at enrollment with the Inflammatory-Rash Overall Built Disability Scale (I-RODS) (range from 0-worst to 48-best) and the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale (range from 0-best to 10-worst); QoL was measured using the EUROQoL-5D-3L scale. The scale consists of 5 domains, each with a score from 1 –best-

to 3 –worst, that measure different aspects of QoL: mobility, self-care, usual activities, pain, anxiety/depression); the EQ VAS (Euro-QoL visual analogue scale) that records the patient's self-rated health on a vertical visual analogue scale, where a score of 100 refers to the best imaginable health state and a score of 0 refers to the worst imaginable health state. The VAS can be used as a quantitative measure of health outcome that reflects the patient's own judgment.

Statistical analysis

Descriptive statistics were performed on the available exposure and outcome variables in the entire sample. Data were reported as frequencies and percentages for categorical variables, and as medians and interquartile ranges for continuous variables. Since most of the patients performing physical activity in our cohort reported to walk while only a minority of them performed other sport activities, physical activity was analyzed considering separately walking and performing other sport activities. The effect of lifestyle and dietary exposures on impairment, disability and QoL was evaluated using logistic regression models. The four outcomes measuring impairment (MRC, ISS) and disability (INCAT, I-RODS) were analyzed separately. For each of the four outcome measures, patients were divided in two groups based on the median of the distribution of the outcome score: 1) from 0 to the median; 2) above the median. The association was then evaluated using logistic regression models. In each model the outcome, categorized as described above, was the dependent variable, and exposures were the independent variables. The probability modeled was that of having a higher level of impairment (MRC, ISS) or disability (INCAT, I-RODS). All models were adjusted for age, sex, disease duration (years), physical activity (yes vs. no) and smoke (yes vs. no). Models with the two disability outcomes (INCAT, I-RODS) as dependent variable were also adjusted for impairment (MRC, ISS). The association of each exposure variable with each different domain of QoL (mobility, self-care, usual activities, pain, anxiety/depression) was evaluated using separate ordinal logistic regression models, with the QoL domain (categorized as 1, 2 or 3) as dependent variable, and exposures as independent variables. For the EQ VAS score, patients were divided into

quartiles, and ordinal logistic regression models, with EQ VAS quartiles as dependent variable and exposures as independent variables, were used to evaluate the impact of each exposure variable on the EQ VAS score. The probability modeled was that of having a good level of QoL. All models were adjusted for age, sex, disease duration (years), physical activity (yes vs. no) and smoking (yes vs. no). Results obtained from each logistic regression model were expressed as odds ratio (OR) with 95% confidence interval (CI). All tests were two-tailed and the significance level was set at 0.05. Statistical analyses were performed with the SAS statistical package, version 9.4 (SAS Institute, Cary, NC, USA).

Results

A total of 323 patients fulfilling the EFNS/PNS criteria for CIDP were included in the analysis. Of these patients, 214 (66%) were males and 109 (34%) were females, with an average age at study entry of 57 years (median 58 years; range 11-89 years), and mean disease duration of 8.5 years (median 6 years; range 0.5-52 years). The description of exposures and outcome variables in the study sample is reported in Table 2. Logistic regression models showed that physical activity was associated with patients performing physical activity had lower impairment measured by ISS and with lower disability measured by INCAT and RODS, while no association was found with MRC (Table 3). Data for QoL were available for 315 patients. Performing any physical activity was associated with higher quality of life measured by the EQ VAS and in all the EURO-QoL domains, except for anxiety/depression (Table 4). None of the remaining exposure variables revealed significant associations. The predominant type of physical activity reported by the sample was walking. Among the 155 patients performing at least one type of physical activity, a total of 64 patients only walked, while 91 were involved in at least one sport activity. A stronger association with a lower disability measured by INCAT was observed for sport activities compared to walking alone, while a similar effect of the two types of physical activity was observed on I-RODS (Table 3). Walking was associated with a lower impairment measured by ISS compared to performing sport

activities, but in both cases the association was not statistically significant (Table 3). When considering the EQ VAS score, and mobility, self-care and pain domains of QoL, the effect of physical activity was mainly driven by sport activities, while the effect of sports on usual activities domain was similar to walking (Table 4). A positive effect on anxiety/depression domain was observed for walking, but not for other sport activities (Table 4).

Discussion

In this study, physical activity was associated with lower sensory impairment, less disability and a better QoL. Although reverse causality may have contributed to the magnitude of the effect for disability, the association remained statistically significant after adjusting the model for the extent of impairment, suggesting that, at the same impairment level, patients who practice physical activity have less disability and better QoL.

Ameliorative effect of physical activity on sensory symptoms has been observed in chemotherapy-induced [25,26] and diabetic neuropathy [27-29], and a recent study showed that physical activity was associated with less sensory neuropathy symptoms and better sensory nerve action potential amplitudes in older men [30]. Potential mechanisms include the anti-inflammatory [31] and the regenerative effect on nerve fibers of physical exercise [26,28,29,32]. Previous studies have not evaluated the impact of physical activity and rehabilitation on the sensory symptoms of patients with inflammatory neuropathies (Table 1).

Our findings are also in line with the results of three previous observational studies showing that supervised aerobic-cycling [12,15], or unsupervised physiotherapist-prescribed community-based aerobic and strengthening exercise [13] are associated with an improvement in disability, fatigue and QoL in people with inflammatory neuropathies. A randomized controlled trial evaluating home-based exercise in patients with different chronic neuropathies including CIDP, found that muscle and grip strength improved significantly [20]. These findings were subsequently

confirmed by a controlled trial and its one-year follow-up study that showed that aerobic or resistance exercise training improved strength and aerobic capacity of CIDP patients [17,18], although even if disability, fatigue, and QoL did not improve [17,18], a finding for which there may be several explanations. The most likely explanation is that in this study Since all participants in this study were treated at home with subcutaneous immunoglobulin as home treatment, it is possible that this might have negatively affected QoL and fatigue [17]. Other explanations are that participants were more severely affected than in the previous interventional studies [12,13] and training programs were not focused on the weakest muscle groups in each patient. In our study, physical activity was not supervised by health personnel in the context of a study, therefore it is possible that each patient chose the type of physical activity most appropriate for his/her disturbances and that this led to a greater impact on disability and QoL.

The mechanisms underlying the improvement of muscle strength following physical activity are unknown but could be due to an anti-inflammatory effect of exercise on the nerve lesions or muscle fiber hypertrophy or increased neural drive [17]. Future studies should investigate these underlying mechanisms in more detail using electroneuronography as well as nerve and muscle imaging. Three observational studies also found a beneficial effect of inpatient and outpatient rehabilitation on strength and fatigue in Guillain Barré syndrome (GBS) [16,19,21] and a randomized controlled trial showed that high intensity multidisciplinary rehabilitation was superior to low intensity rehabilitation in improving disability in people with GBS several years after recovery [14].

Several studies have shown an association of diet, cigarette, alcohol consumption, and toxic agents exposure with the progression of disability and QoL in different autoimmune disorders [2-11]. We did not find an association between any of these environmental factors and the impairment, disability and QoL of patients with CIDP. One possible explanation is that the questionnaire used in our study was not able to capture the quality of diet by assessing intake of each food instead of

estimating the overall dietary quality by using indicators of compliance with dietary recommendations. Future studies should evaluate the impact of diet in the progression of CIDP by using a specific questionnaire designed to capture healthy eating such as adherence to Mediterranean style diet. We also did not find an association between rice and fish consumption and impairment and disability, suggesting that these dietary factors influence the risk of CIDP but not its severity [22].

Limitations of our study include the use of a non-validated lifestyle and dietary habits questionnaire. In addition, this was an observational cross-sectional retrospective study that cannot prove causality but supports previous interventional studies showing that regular exercise may have an impact on disability and QoL in CIDP. Last, as this is not a population-based study, our findings might be affected by selection bias. Further epidemiological and intervention studies are needed to confirm our results in order to support a possible role of physical activity as part of a secondary preventive strategy.

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Compliance with ethical standards

Conflicts of interest/Competing interests

Pietro Emiliano Doneddu has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Dario Cocito has received honoraria for lecturing from Shire, CSL Behring, and Kedrion and travel grants to attend scientific meeting from Shire, Kedrion, and CSL Behring. Fiore Manganelli reports personal fees for scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Raffaella Fazio has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Chiara Briani has served on scientific advisory boards for Pfizer, Alnylam, and Akcea, and has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Massimiliano Filosto has served on scientific advisory boards for CSL Behring and has received travel grants from Kedrion, Baxter and CSL Behring to attend scientific meeting. Stefano Jann has received research grants from Grifols, outside this work, and travel grants from Grifols and Kedrion. Anna Mazzeo has received travel grants from Kedrion and CSL Behring to attend scientific meeting. Giuseppe Cosentino has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Andrea Cortese has received travel grants to attend scientific meetings from Kedrion. Marinella Carpo has received travel grants to attend scientific meetings from Kedrion. Guido Cavaletti has received honoraria for lecturing and travel grants to attend scientific meetings from Kedrion. Ettore Beghi reports grants from UCB-Pharma, grants from Shire, grants from Eisai, personal fees from Viropharma, grants from Italian Ministry of Health, grants from Fondazione Borgonovo, grants from Associazione IDIC 15, grants from European Union, outside the submitted work. Giuseppe Liberatore has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Lucio Santoro reports personal fees for

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Ethics approval

The study was approved by the Ethical Committee of each participating Center

Consent to participate

Written informed consent was obtained from all participants at enrollment

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