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ORIGINAL COMMUNICATION

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 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 smoking. 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 symptom 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.

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

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.

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Table 1 Previous studies evaluating the beneficial effect of physical activity or rehabilitation in inflammatory neuropathies

References	Participants	Design	Intervention	Outcome	Case no	Main finding
[20]	CIDP, Chronic neuropathies	Prospective randomized controlled trial	Home exercise program	AMS, grip strength, fVC, 30-ft walk, SF-36	21	Improvement in AMS and grip strength
[12]	GBS, CIDP	Observational study	12-week bicycle exercise training	FSS, RAM, FIS, GBS disability score, HADS, RHS, SF-36	40	Improvement in FSS, FIS, HADS, RHS, Sf-36
[15]	GBS, CIDP	Observational study	12-week physical exercise program	VO2peak, POpeak, FSS, AM, SF-36, FIS, RHS, HADS	20	Improvement in POpeak, VO2peak, FSS, FIS, HADS, RHS
[13]	GBS, CIDP, and healthy controls	Observational study	12-week strengthening, aerobic and functional exercise program	ODSS, SF-36, HADS, FSS, cIKS	26	Improvement in ODSS, SF-36, HADS, FSS, cIKS
[14]	GBS in later stages of recovery	Single blind randomized controlled trial	High- vs low-intensity multidisciplinary ambulatory rehabilitation program over 12 months	FIM, WHOQoL-BREF, DASS, PIPP	69	More significant improvement in FIM and PIPP with higher intensity rehabilitation
[19]	GBS	Observational study	Comprehensive individually tailed rehabilitation	MRC, FIM, 6-MWT, 10-min walking test	45	Improvements in all outcome measures
[16]	GBS	Observational study	Inpatient rehabilitation	FIM	1079	Improvement in all the three domains of the FIM
[17]	CIDP	Controlled trial	Aerobic or resistance exercise training for 12 weeks, followed by the other training regimen	VO2-max, cIKS, 6-MWT, ODSS, FSS, SF-36	17	Improvement in VO2-max and cIKS
[18]	CIDP	Observational study	One-year follow-up after aerobic or resistance exercise training for 12 weeks, followed by the other training regimen	VO2-ma, cIKS, 6-MWT, ODSS, FSS, SF-36, MRC	10	Patients that continued aerobic and resistance exercise preserved their cIKS and VO2-max gains after one year of follow-up
[21]	GBS	Observational study	Inpatient rehabilitation	MRC, GBS disability score, ability to walk	40	Improvement in MRC, GBS disability score, and ability to walk

AM actual mobility, *AMS* average muscle score, *CIDP* chronic inflammatory demyelinating polyradiculoneuropathy, *cIKS* isokinetic muscle strength, *DASS* Depression Anxiety Stress Scale-21, *FIM* functional independence measure, *FIS* Fatigue Impact Scale, *FSS* Fatigue Severity Scale, *ft* feet, *fVC* forced vital capacity, *GBS* Guillain–Barré syndrome, *HADS* Hospital Anxiety And Depression Scale, *MRC* Medical Research Council, *ODSS* Overall Disability Sum Score, *PIPP* perceived impact problem profile, *POpeak* peak power output, *QoL* quality of life, *RAM* Rotterdam Activity Monitor, *RHS* Rotterdam Handicap Scale; *SF-36* Short-Form 36, *VO2-max* maximal oxygen consumption velocity, *WHOQoL-BREF* World Health Organization Quality of Life, *6-MWT* 6-min-Walk Test

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 enrollment, 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 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 drug 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, ≥ 10 drinks per day on average), regular physical activity (type [walking for at least 30 min, 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), and 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) sum score on 12 muscles (rangingfrom 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 five 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 analog scale) that records the patient's self-rated health on a vertical visual analog 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 into 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 variables 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 patients performing physical activity had lower impairment measured by ISS and 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). 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

Table 2 Descriptive statistics of exposure and outcome variables

Exposures	*n*	%
Exposure to toxic agents		
No	261	81.1
Yes	61	18.9
NA	1	
Physical activity		
No	168	52.0
Yes	155	48.0
Type of physical activity		
Walking	103	31.9
Running	10	3.1
Swimming	29	9.0
Cycling	34	10.5
Gym	34	10.5
Team sport	5	1.6
Other sport	12	3.7
Smoke		
No	166	51.4
Yes	157	48.6
Regular alcohol consumption		
No	204	63.2
Yes	119	36.8
Illegal substances consumption		
No	311	98.7
Yes	4	1.3
NA	8	
Dietary restrictions		
No	298	92.3
Yes	25	7.7
Dietary regimen		
Omnivorous	320	99.1
Vegetarian	3	0.9
Impairment	Median	IQR
MRC score	56	52–60
ISS score	4	2–8
Disability	Median	IQR
INCAT score	2	1–4
I-RODS score	35	26–42
EURO-QOL-5D-3L ($n=315$)	*n*	%
Mobility		
1	86	27.3
2	221	70.2
3	8	2.5
Self-care		
1	194	61.6
2	111	35.2
3	10	3.2
Usual activities		
1	124	39.4
2	181	56.0
3	10	3.1

Table 2 (continued)

Exposures	*n*	%
Pain/discomfort		
1	137	43.5
2	168	53.3
3	10	3.2
Anxiety/depression		
1	156	49.6
2	145	46.0
3	14	4.4
EQ VAS (quartiles)		
1 (0–49)	51	17.4
2 (50–59)	62	21.1
3 (60–74)	106	36.0
4 (75–100)	75	25.5
NA	21	

INCAT Inflammatory Neuropathy Cause and Treatment disability scale, *IQR* interquartile range, *I-RODS* Inflammatory-Rash Overall Built Disability Scale, *ISS* INCAT sensory scale, *MRC* Medical Research Council, *EQ VAS* Euro-QoL visual analogue scale, *NA* not available

Table 3 Association of physical activity with impairment and disability

	OR	95% CI	*p* value
Any physical activity			
INCAT	0.58	0.35–0.99	0.0476
I-RODS	0.44	0.26–0.75	0.0023
MRC	1.28	0.82–2.00	0.2853
ISS	0.62	0.40–0.98	0.0421
Only walking			
INCAT	0.74	0.37–1.47	0.3933
I-RODS	0.47	0.23–0.78	0.0335
MRC	1.63	0.90–2.96	0.1098
ISS	0.58	0.31–1.05	0.0727
At least one sport activity			
INCAT	0.49	0.26–0.92	0.0267
I-RODS	0.41	0.22–0.78	0.0060
MRC	1.07	0.64–1.82	0.7852
ISS	0.66	0.39–1.13	0.1307

CI confidence interval, *INCAT* Inflammatory Neuropathy Cause and Treatment disability scale, *I-RODS* Inflammatory-Rash Overall Built Disability Scale, *ISS* INCAT sensory scale, *MRC* Medical Research Council, *OR* odds ratio

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.

Table 4 Association of physical activity with quality of life

	OR	95% CI	*p* value
Any physical activity			
Mobility	2.01	1.20–3.35	0.0073
Self-care	2.05	1.28–3.29	0.0030
Usual activities	2.17	1.37–3.45	0.0010
Pain	1.91	1.21–3.02	0.0053
Anxiety/depression	1.41	0.90–2.20	0.1316
EQ VAS (quartiles)	2.08	1.36–3.19	0.0008
Only walking			
Mobility	1.94	0.95–3.96	0.0673
Self-care	1.79	0.94–3.42	0.0787
Usual activities	2.62	1.39–4.95	0.0030
Pain	1.45	0.80–2.63	0.2260
Anxiety/depression	1.94	1.07–3.53	0.0298
EQ VAS (quartiles)	1.97	1.12–3.47	0.0183
At least one sport activity			
Mobility	2.57	1.37–4.81	0.0033
Self-care	3.23	1.69–6.20	0.0004
Usual activities	2.42	1.37–4.29	0.0025
Pain	2.45	1.41–4.26	0.0014
Anxiety/depression	1.14	0.67–1.93	0.6239
EQ VAS (quartiles)	2.31	1.39–3.83	0.0012

CI confidence interval, *OR* odds ratio, *EQ VAS* Euro-QoL visual analog scale

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], is 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 1-year follow-up study that showed that aerobic or resistance exercise training improved strength and aerobic capacity of CIDP patients [17, 18], even if disability, fatigue, and QoL did not improve [17, 18]. Since all

participants in this study were treated at home with subcutaneous immunoglobulin, it is possible that this has 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.

Several studies have shown an association of diet, cigarette, alcohol consumption, and toxic agent 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 may influence the risk of CIDP, but not its severity [22].

The limitations of our study include the use of a non-validated lifestyle and dietary habit 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. It is also possible that CIDP patients that are severely disabled and impaired might not be able to perform physical activities and sport. 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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Author contributions PED designed and conceptualized the study, had a major role in the 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, and 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 and LS contributed to the study conception and design, had a major role inacquisition and interpretation of data and revised the manuscript for intellectual content. ENO conceived, organized and designed the study, reviewed and commented on the statistical analysis and reviewed the report.

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

Compliance with ethical standards

Conflicts of interest Pietro Emiliano Doneddu has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Dario Cocito has received honoraria for lecturing fromShire, 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 and 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 scientific events from CSL Behring and has received travel grants to attend scientific meetings from CSL Behring and Kedrion. Erdita Peci has received travel grants to attend scientific meetings from CSL Behring. Eduardo Nobile Orazio reports personal fees for Advisory or Scientific Board from Kedrion, Italy, Baxter, Italy, Novartis, Switzerland, CSL-Behring, Italy, Astellas, the Netherlands, outside the submitted work and travel grants to attend Scientific Meeting from Baxter, Grifols, Kedrion, and Novartis, Italy. The other authors declare no conflict of interest.

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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