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ORIGINAL REPORT

ANALYSING THE FAVOURABLE EFFECTS OF PHYSICAL EXERCISE: RELATIONSHIPS BETWEEN PHYSICAL FITNESS, FATIGUE AND FUNCTIONING IN GUILLAIN-BARRÉ SYNDROME AND CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Objective: **To elucidate the effects of physical exercise in severely fatigued patients with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy, and to clarify the mutual relationships between 5 domains studied in these patients: physical fitness, fatigue, objectively measured actual mobility, perceived physical functioning, and perceived mental functioning.**
Design: **Case series.**
Subjects/patients: **Twenty patients with Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.**
Methods: **The patients undertook a 12-week physical exercise program. Relationships between domains were studied in the change scores, and additionally in the baseline data of patients. The percentage of significant relationships between each pair of domains was determined.**
Results: **In the change scores, a small percentage of significant relationships was found between the physical fitness domain and the other 4 domains (2/30, 7%). A higher percentage of significant relationships was found between the domains perceived mental functioning and actual mobility (44%), perceived mental functioning and perceived physical functioning (44%), and between fatigue and perceived physical functioning (33%). Generally, similar patterns were found in the baseline data.**
Conclusion: **Changes in fatigue, actual mobility and perceived functioning seem not to be influenced by changes in physical fitness. This study stresses the presence and importance of additional effects of a physical training program, not directly related to increasing fitness.**

Key words: physical exercise, physical fitness, fatigue, activities of daily living, acute inflammatory polyradiculoneuropathy.

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INTRODUCTION

Guillain-Barré syndrome (GBS) is an immune-mediated polyradiculoneuropathy affecting 1–2 per 100,000 of the population (1). Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may be considered a chronic variety of GBS. Although the majority of patients with GBS experience rather good neurological recovery, severe fatigue is an important residual and disabling complaint, seriously affecting quality of life (2).

Aerobic training is generally focused on increasing physical fitness, and it is widely accepted that, in this way, other beneficial effects are also obtained (3), on mood, depression or mental functioning (4, 5). It was hypothesized that a 12-week physical exercise program might also have different positive effects in severely fatigued patients with GBS and CIDP. Therefore, a non-controlled training study was conducted in 20 severely fatigued patients (6). Outcome measures represented the different parts of the International Classification of Functioning, Disability and Health (ICF) (7). Except for actual mobility, statistically significant and clinically relevant differences were found between the post- and pre-training measurements, and between patients and control subjects (6).

In addition to assessing the effect of training, the aim was to obtain insight into the mechanisms behind the training effects. At the start of the study a hypothetical model about the mechanisms of action was created (Fig. 1). For that purpose, 5 domains were defined: physical fitness, self-reported fatigue, actual mobility (i.e. objectively measured functioning, defined by body postures and motions), perceived physical functioning (i.e. perceived problems with physical functioning) and

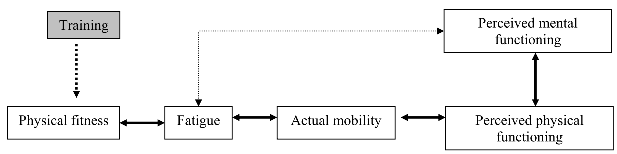

Fig. 1. Hypothetical model of the mechanisms of action.

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perceived mental functioning (i.e. perceived problems with psychological / mental functioning). However, the evaluation part of the study did not focus on the mechanisms.

The aim of the present study, therefore, was to clarify the mutual relationships between the 5 domains, and to obtain insight in the mechanisms of the effects of physical exercise. Relationships were studied in the change scores (differences between baseline and post-training), supported by cross-sectional analysis of the baseline data of patients.

METHODS

Patient selection, inclusion and exclusion criteria, training intervention, measurement protocol, instruments and outcome measures are described in more detail elsewhere, as are the results of the intervention part of the study (6). These results are summarized in Table I.

Subjects

Sixteen neurologically "relatively well–recovered" patients with GBS and 4 neurologically stable patients with CIDP participated in the training study (14 women, 6 men, median age 49 years) (6). All patients were severely fatigued (defined as Fatigue Severity Scale Score ≥5, (2), neurologically stable (defined as no apparent changes in GBS disability score for at least 3 months), and all patients were screened to exclude other possible explanations for their fatigue complaints (6). The study was approved by the Ethics Committee of Erasmus Medical Center.

Intervention

The training program for the patient group consisted of 3 supervised cycle training sessions per week, during a 12-week period (6).

Instruments and outcome measures

Patients underwent all measurements at baseline and after the training program. Outcome measures were categorized into the 5 domains described above. Not all measured and calculated outcome measures were included in the analyses of the present study. Criteria used for selecting or rejecting a single outcome measure were: the degree to which an outcome measure was assessed to fit or represent a specific domain, a preference for summary scores compared with sub-scores and, finally, as far as possible, a balance in number of outcome measures for each of the 5 domains.

Physical fitness

Peak oxygen uptake (ml/kg/minute) and peak power output (W) were determined using an incremental, adaptive cycle ergometer test (Jaeger, Breda, The Netherlands), during which heart rate and gas exchange, including oxygen uptake, was registered continuously with the K4b^2 exercise testing system (Cosmed Srl., Rome, Italy). The highest physical load level (peak power output, POpeak) and the mean oxygen uptake (VO_2peak) during the last 30 seconds of the highest load level were included as outcome measures. To assess muscular power, knee extensors and flexors were measured bilaterally with a computerized muscle force measurement device (Biodex, Biometrics Europe, Almere, The Netherlands). Subjects performed 10 flexion and 10 extension movements with each leg, with maximal concentric contractions at 2 angular speeds (60°/second and 180°/second). For the present analysis, the average power (W) of all flexion and extension contractions at the 2 speeds was used.

Fatigue

Fatigue was assessed with the Fatigue Severity Scale (FSS), a 9-item questionnaire with answers ranging from 1 to 7. The FSS score is calculated as the mean item score, ranging from 1 ("no signs of fatigue") to 7 ("most disabling fatigue") (2, 8).

Actual mobility

Actual mobility during normal daily life was measured objectively using an Activity Monitor (AM) (9, 10). The AM, based on body-fixed accelerometers and a portable recorder (Vitaport technology, TEMEC Instruments, Kerkrade, The Netherlands) has been extensively validated and used before. To obtain comparable data in our patients, a period of 24 hours' consecutive recording time (03.00 h till 03.00 h the next day) was extracted for statistical analysis. Three AM outcome measures were included in the present analysis: the percentage of time a patient was active (e.g. walking, cycling, climbing stairs, and general movement), the percentage of time a patient was active or standing, and

Table I. *Mean values (SD) or median [25–75 percentile] of the variables used in the analysis of this paper at baseline and post-training, and their differences*

Domains and outcome measures	Baseline	Post-training	Differences
Physical fitness			
Peak oxygen uptake (ml/kg/min)	25.7 (8.1)	30.7 (9.7)	5.0 (6.0)*
Peak power output (W)	133.3 (37.6)	171.9 (53.2)	38.6 (28.5)*
Muscular fitness (W)	56.8 (23.4)	64.0 (25.4)	7.2 (7.9)*
Fatigue			
FSS (scores)	6.1 [5.4–6.7]	5.4 [3.6–5.8]	–1.0 [–2.2 to –0.3]*
Actual mobility			
Percentage active	10.7 (3.6)	11.2 (4.0)	0.5 (2.6)
Percentage active and standing	25.8 (8.9)	25.0 (7.6)	–0.8 (7.7)
Body motility (g)	0.0111 (0.002)	0.0119 (0.003)	0.0008 (0.003)
Perceived physical functioning (scores)			
SF36–physical	45.0 [37.4–51.7]	50.8 [39.3–56.4]	4.9 [–3.8–11.6]*
FIS–physical	2.30 [1.48–2.68]	1.00 [0.35–1.50]	–1.10 [–1.68 to –0.35]*
Rotterdam Handicap Scale	3.56 [3.44–3.89]	3.89 [3.56–4.00]	0.11 [0.00–0.22]*
Perceived mental functioning (scores)			
HAD	3.50 [3.11–4.32]	3.00 [2.68–3.32]	–0.50 [–1.04 to –0.14]*
SF36–mental	50.9 [44.5–54.5]	55.9 [51.0–58.4]	3.5 [–4.6–12.0]
FIS–cognition	1.55 [0.30–2.20]	0.30 [0.00–1.40]	–0.55 [–0.98 to –0.10]*

*Post-training data compared with baseline data, $p<0.05$ (Wilcoxon signed-rank test).

FSS: Fatigue Severity Scale; SF-36: 36-Item Short Form Health Survey; FIS: Fatigue Impact Scale; HAD: Hospital Anxiety and Depression Scale.

the body motility value, which can be regarded as being related to the overall level of physical activity during the measurement (9).

Perceived physical functioning

Perceived physical functioning was calculated using the 36-Item Short Form Health Survey (SF-36). The items are categorized into 8 subscales, and from these subscales, a physical and mental summary score was calculated (11–13). In this domain, the physical summary score was used. The Fatigue Impact Scale (FIS) is a 40-item questionnaire with answers ranging from 0 ("no problem") to 4 ("extreme problem"). For this domain, the physical subscale (10 items) was used (14, 15). Additionally, the Rotterdam Handicap Scale (RHS) was used. The RHS is a 9-item health status questionnaire, focusing mainly on physical aspects, with answers on each inquiry ranging from 1 ("unable to fulfil tasks/activities") to 4 ("complete fulfilment of tasks/activities") (16).

Perceived mental functioning

Perceived mental functioning was calculated using the Hospital Anxiety and Depression Scale (HAD) (17, 18). A second outcome measure within this domain was the mental summary score of the SF-36 (11–13). The cognitive subscale (10 items) of the FIS was selected as a third and final outcome measure of mental functioning (14, 15).

Data analysis

Each domain was represented by 3 outcome measures, except for the fatigue domain (FSS score only, see also Table I). Pearson correlation coefficients were calculated between all outcome measures of different domains. If a p-value of a correlation coefficient was <0.1 (which was considered the most appropriate value, because of the relatively small number of patients and the purpose of the study) a relationship was considered significant. In this way the number and percentage of significant relationships between domains could be calculated, which was assumed to reflect the strength of the relationship between 2 domains.

RESULTS

The correlation coefficients between all outcome measures are shown in Table II. In the change scores, only 2 out of 30 (2/30, 7%) relationships of physical fitness with other domains were significant. More significant relationships were found between perceived mental functioning and actual mobility (4/9, 44%), between perceived mental functioning and perceived physical functioning (4/9, 44%), and between fatigue and perceived physical functioning (1/3, 33%). The cross-sectional data showed the same patterns, although the relationship between perceived mental and physical functioning was less strong (2/9, 22%). In contrast to the change scores, a rather strong relationship (4/9, 44%) was found between physical fitness and physical functioning.

DISCUSSION

The aim of this study was to clarify the mutual relationships between different outcome domains, and to obtain insight into how a training program affects fatigue and different types of actual and perceived functioning. The training study showed significant improvements in physical fitness and in most other outcome measures when comparing baseline and post-training values (6). The aim of the training program was mainly to improve physical fitness: it was assumed that this should lead to changes in other domains, for example as expressed in Fig. 1. However, detailed data analyses as performed in the present study, showed only a very limited number of signifi-

Table II. *Correlation coefficients between all outcome measures, categorized according to the 5 domains. The coefficients of change scores are shown in the upper-right of the table, the cross-sectional data in the lower-left. Significant relationships between outcome measures of different domains are highlighted in bold*

	Physical fitness			Fatigue	Actual mobility			Perceived physical functioning			Perceived mental functioning		
	VO_2peak	POpeak	Pmusc	FSS	%act	%act+ stand	Motility	SF36phys	FISphys	RHS	HAD	SF36ment	FIScog
VO_2peak	×	0.53**	0.63***	–0.36	–0.10	–0.22	–0.20	0.07	–0.16	0.22	0.24	0.17	0.17
POpeak	0.77***	×	0.22	–0.16	–0.16	–0.17	–0.06	0.29	–0.16	0.03	0.00	–0.04	0.13
Pmusc	0.63***	0.79***	×	–0.30	0.14	–0.08	–0.27	0.08	0.37	0.15	**0.54****	0.16	**0.57****
FSS	–0.31	–0.19	0.26	×	–0.04	0.09	0.30	**–0.47***	0.09	0.21	–0.02	0.24	0.25
%act	**0.45***	**0.51****	0.36	–0.13	×	0.75***	0.71***	0.34	**0.54****	–0.37	**0.58****	**–0.49***	0.06
%act+ stand	0.19	0.10	0.18	0.11	0.72***	×	0.59**	0.19	0.38	**–0.49****	**0.49****	**–0.44****	0.00
Motility	–0.10	–0.31	–0.23	–0.16	0.29	0.52**	×	0.17	0.16	–0.33	0.23	–0.35	–0.03
SF36phys	0.27	**0.54****	0.18	**–0.51****	0.18	–0.04	–0.23	×	0.06	–0.25	0.00	**–0.45***	–0.18
FISphys	–0.20	–0.15	0.11	**0.65*****	–0.16	0.14	–0.17	–0.51**	×	–0.41*	**0.61*****	**–0.61****	**0.55****
RHS	**0.56****	**0.67*****	**0.56****	–0.35	0.16	–0.07	–0.29	0.29	–0.20	×	–0.25	0.40	0.02
HAD	0.24	0.11	0.19	0.28	**0.40***	**0.43***	0.39	–0.30	0.14	–0.12	×	–0.59**	0.66***
SF36ment	–0.31	–0.30	–0.11	0.15	**–0.48***	–0.38	**–0.41***	**–0.40***	0.32	0.16	–0.63***	×	–0.40
FIScog	0.10	0.08	0.21	0.38	–0.25	0.00	–0.12	–0.33	**0.48****	0.16	0.43*	0.01	×

*0.05<p<=0.1; **0.01>p<=0.05; ***p<0.01.

n per cell may vary from 17 to 20.

VO_2peak: peak oxygen uptake; POpeak: peak power output; Pmusc: muscle power; FSS: Fatigue Severity Scale; %act: percentage active per 24 hours; % act+stand: percentage active and standing per 24 hours; SF36phys: physical summary score of the 36-item Short Form Health Survey, FISphys: physical subscale Fatigue Impact Scale; RHS: Rotterdam Handicap Scale; HAD: Hospital Anxiety and Depression Scale; SF36ment: mental summary score of the 36-item Short Form Health Survey; FIScog: cognitive subscale of the Fatigue Impact Scale.

cant relationships between physical fitness and other domains, especially in the changes scores, but also in the baseline data, strongly suggesting that physical fitness is not the main determinant of functioning in these patients. Training resulted in improved fitness, but improvements in perceived fatigue and functioning do not seem to be significantly influenced by improved fitness. Fig. 2 shows the major relationships of the change scores. Although the design of the current study does not allow statements on causal relationships, the most plausible explanation is the important role of psychological factors: attention of researchers and physical therapists provided to the patients, increased self-confidence, and the social aspect of the training program might be all important factors. If so, a physical training program such as that used in our study may have a dual effect: not only improving fitness, but also directly changing mental functioning and, by this means, other domains of functioning. This explanation was supported by the subjective impression of the researchers and physical therapists involved in this study. The observation that physical training has a positive effect on mood and mental functioning has been described previously. For example, a review article by Lett et al. (4) described positive effects of exercise on mood in patients with coronary heart disease. In another review article it was reported that exercise therapy results in a slightly favourable effect on depression in chronic fatigue syndrome patients compared with control subjects (5). However, the very weak relationships in the change scores between physical fitness and other domains remains surprising.

There were also some other remarkable findings. There were relatively many significant relationships between perceived mental functioning and objectively measured actual mobility. The positive relationship between these domains is reported frequently (e.g. 19, 20). However, in the present study, inverse relationships were generally found between actual mobility and mental functioning, both in the cross-sectional data and in the change scores. In the cross-sectional data, a higher level of mental functioning was associated with a lower level of actual mobility. This relationship may be a consequence of patients trying to maintain their normal activity level, while their capability is lowered by (subclinical) neurological deficits. This might even result in more complaints of fatigue, and subsequently in decreased physical and mental functioning; actually a matter of overload (19). More detailed analysis of the inverse relationship in the change scores showed that persons with a relatively high level of actual mobility at baseline (and therefore with a relatively low level of mental functioning) became less active and improved strongly in mental functioning after the training period, whereas persons with a relatively low level of actual mobility at baseline (and therefore with a relatively high level of mental functioning) became more active and showed a fair improvement in mental functioning. This suggests that subgroup-specific effects of training may exist, and also that a training program has to be adapted to specific subgroups. Furthermore, a clear relationship was found between perceived fatigue and perceived physical functioning. This can be attributed to their actual mutual relationship, but partly also to instrument characteristics: the FSS evaluates the perceived severity of fatigue, but via the impact of fatigue on physical functioning.

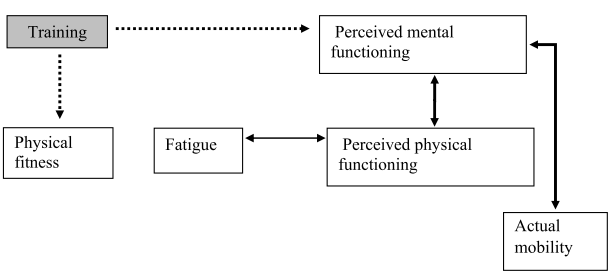

Fig. 2. Model resulting from the change scores of the current study. Thickness of the lines between domains represents the strength of the relationships.

This study is not without limitations. Firstly, the methodology (e.g. small number of patients, selecting specific outcome measures, counting number of relationships) may be highlighted. However, we feel that the number of patients is not a crucial factor. The fact that even in this relatively small group significant differences were found between follow-up and baseline indicates that issues of reliability, sensitivity to change and type-II error were not dominantly present. Furthermore, additional methods of data analysis, e.g. taking other outcome measures, other ways of examining relationships, showed that the main conclusions do not change when using other methods. A second point concerns validity: the question as to whether instruments are adequately chosen, and the degree in which outcome measures represent a specific domain. We were careful in this process, and choices of instruments and domains were based on literature (e.g. validity studies) and thorough examination of the measurement instruments, the items and outcome measures. Finally, the data of the present study are not completely independent: outcome measures within a domain can and will be related (see also Table II), and the change scores will not be independent of the baseline data. Although data analysis showed that dependencies exist, they are not that strong that the data can be regarded sufficiently valid. Therefore, we feel that, despite these limitations, the main conclusions of this study are valid.

The main conclusion of this study is that a poor relationship exists between (changes in) physical fitness and (changes in) other functional measures. Physical training in patients with GBS and CIDP, aiming to increase physical fitness, has positive effects on physical fitness, fatigue and most functional outcome measures, but changes in fatigue, actual mobility and perceived functioning seem not to be influenced by changes in physical fitness. Therefore, this study stresses the presence and importance of additional effects of a physical training program, not directly related to increasing fitness.

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