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A 5-Year Longitudinal Study of Fatigue in Patients With Late-Onset Sequelae of Poliomyelitis

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ABSTRACT.

Objectives: To study the severity and 5-year course of fatigue in patients with late-onset sequelae of poliomyelitis (LOSP) and to identify physical and psychosocial determinants of fatigue.

Design: Prospective cohort study with 5 measurements over 5 years.

Setting: University hospital.

Participants: Patients with LOSP (N=168); 89% of the subjects completed the study.

Interventions: Not applicable.

Main Outcome Measures: Fatigue assessed with the Fatigue Severity Scale (FSS). Potential determinants were perceived physical functioning, bodily pain and mental health, extent of paresis, walking capacity, comorbidity, sleeping disorders, coping, and social support. Associations were investigated by multivariable longitudinal analysis using generalized estimating equations.

Results: The mean FSS score $\pm$ SD at baseline was 5.1 ± 1.4 , which did not change significantly during the 5-year follow-up.

Reduced physical functioning, increased bodily pain, reduced sleep quality, more psychologic distress, and higher task-oriented coping were independently associated with fatigue.

The extent of paresis and walking capacity were strongly associated with physical functioning.

Conclusions: Fatigue is severe and persistent in patients with LOSP due to physical and psychologic factors, which has implications for counseling and treatment. In addition to the commonly applied interventions targeting physical aspects, psychologic interventions are a potential area for reducing fatigue.

MANY POLIO SURVIVORS develop postpolio syndrome (PPS), a condition characterized by new neuromuscular symptoms, after many years of stable functioning. The newly developed symptoms can include progressive muscle weakness or increased muscle fatigability, with or without generalized fatigue, diminished functional capacity, cold intolerance, and muscle and joint pain.¹ Patients with PPS report fatigue as their most frequent and most debilitating complaint, with a reported incidence of 34% to 87%.²⁻⁶ Fatigue in PPS is often severe, sometimes interfering with activities of daily life and leading to restrictions in participation in social activities and limitations in work duties.³ Greater insight into the factors that contribute to fatigue is needed to design targeted intervention strategies aimed at reducing fatigue in patients with PPS.

Several studies have reported on the physical and psychologic factors that contribute to fatigue.⁷⁻¹⁰ There are positive correlations between fatigue and physical variables, such as disuse and overuse of muscles and

pain, as well as with psychologic variables, such as depression.^{4,8,9} A crosssectional study showed that vitality (or the absence of general fatigue) in PPS is explained mainly by physical functioning, physical fatigue, pain, and body mass index rather than by psychologic factors like mental health and mental fatigue.¹⁰ Notably, factors that impact fatigue have the potential for providing treatment opportunities. For example, physical factors might be addressed with exercise training and physical therapy aimed at enhancing exercise capacity and physical functioning. For psychologic factors, a cognitive behavioral approach may reduce fatigue symptoms in PPS as in other diseases, such as multiple sclerosis.¹¹ The Comorbidity and Aging effects in Rehabilitation Patients on Activities (CARPA) study is a prospective and ongoing follow-up study to investigate the course of functioning in patients with late-onset sequelae of poliomyelitis (LOSP) with specific emphasis on the influence of comorbidity and aging.^{12,13} The term LOSP is used rather than PPS because PPS implies the exclusion of comorbid conditions as causes of muscle weakness and fatigue.¹ To date, physical, psychologic, and social factor data have been collected from 168 patients over a period of 5 years. The CARPA study provides a unique opportunity to study fatigue in a large sample using a longitudinal study design. The aims of the present study were to [table 1] characterize the severity, course, and physical and psychosocial variables related to fatigue in patients with late-onset sequelae of poliomyelitis (LOSP).

METHODS

Participants

The study group, which consisted of 168 subjects with LOSP, is described in detail elsewhere.¹² The inclusion criteria for the study were as follows: (1) history of poliomyelitis anterior acuta; (2) the presence of residual paresis in at least 1 extremity; (3) at least 1 consultation with a neurologist or specialist in physical medicine and rehabilitation during the previous 5 years for late-onset symptoms; (4) 45 to 85 years of age; and (5) no medical condition indicating a life expectancy of less than 1 year. The study was approved by the medical ethics committees of the 2 participating university hospitals. All participants provided informed written consent. The baseline characteristics of the study group are summarized in table 1.

Assessments

Five assessments were performed over 5 years: at baseline, and after 1, 2, 3, and 5 years. Each assessment involved completing questionnaires at home and being interviewed and tested at the hospital by a doctor who was not involved in the patient's routine treatment. If patients were not able to visit the outpatient clinic, they were interviewed by phone or visited at home.

Instruments

The Fatigue Severity Scale (FSS) measures subjective fatigue and is composed of 9 statements that are rated on a scale from 1 (strong disagreement) to 7 (strong agreement). The score is calculated as the mean of the responses to the 9 statements. There is a maximal score of 7, and a score greater than 4 indicates a moderate to high level of fatigue.¹⁴ The FSS has good internal consistency.¹⁵ The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is a self-administered health-related quality of life inventory with 36 questions in 8 physical and psychologic domains.¹⁶ The domain scores range from 0 to 100, with a higher score indicating higher levels of functioning or wellbeing.

The SF-36 has been translated and validated for the Dutch population.¹⁷ This study used the following domains: physical functioning, bodily pain, and mental health.

The extent of paresis was assessed with a strength sum-score calculated from manual muscle tests according to the Medical Research Council scale; the strength sum-score includes 16 leg-muscle groups and 10 arm-muscle groups (score range, 0–130) and was described previously by Nollet,⁶ Meldrum,¹⁸ and colleagues.

Walking capacity was determined by measuring the distance covered during a 2-minute walking test at self-preferred speed on an indoor circuit. This test has excellent test-retest reliability and has been recommended as a capacity qualifier of physical functioning for patients with LOSP.¹⁹ Comorbidities were assessed with the Cumulative Illness Rating Scale (CIRS). The CIRS rates 13 body systems using a 5-point

(pathophysiologic) severity scale, with 0 being no disease and 4 being a life-threatening disease. A sum score was calculated as an aggregate measure of comorbidity (comorbidity count). The CIRS is a valid and reliable method of measuring comorbidities that can be used in clinical research.²⁰ Sleep disorders were assessed using the Nottingham Health Profile, a self-administered questionnaire that measures health status.²¹ The Nottingham Health Profile domain sleep consists of 5 questions with a score ranging from 0 (no complaints) to 100 (indicating very poor sleep).

Coping was measured using the Coping Inventory for Stressful Situations Short Form, which has 21 questions that are scored using a 5-point scale. The Coping Inventory for Stressful Situations is composed of 3 scales that relate to different styles of coping: task-oriented coping, emotional coping, and avoidance. A higher scale score indicates that the particular coping style is used more often.²² Social support was assessed with the questionnaire Social Support Scale (in Dutch), which consists of 12 questions scored on a 5-point scale. The total score is calculated and ranges from 12 (no social support) to 60 (good perceived social support).²³

Data Analysis

Demographic data were analyzed with descriptive statistics.

The time course of changes in fatigue during the 5-year study was analyzed with linear generalized estimating equations (GEE), a linear regression analysis that takes into account the dependence of the observations within an individual subject over time and allows inclusion of subjects with missing data.

The correlation structure was set at exchangeable (ie, correlation coefficients between the first and 4 successive assessments are approximately equal). In all regressions, time was modeled as a continuous variable that was expressed in years. The impact of new muscle weakness and/or new muscle fatigue at baseline on the time course of fatigue was tested using the interaction term time by new neuromuscular symptoms. Variables that were potentially associated with fatigue were analyzed with multivariable repeated-measures models. To determine whether a variable should be included, separate univariate models were tested in which only 1 variable was added to the model at a time. When a variable was significantly correlated with fatigue ($P<.01$), it was included in the final model.

Univariate associations between the potential variables were determined to assess multicollinearity. In case of a correlation of 0.75 or higher, the variable with the lowest correlation with fatigue was omitted. The identified variables were entered into the overall multivariable regression model. GEE analyses were performed using STATA (version 9.0).^a

RESULTS

During the course of the study, 5 patients died (2 patients of unknown causes, 1 patient of lung carcinoma, 1 patient of adrenal gland carcinoma, and 1 patient of complications during treatment for lymphoma). Two patients died after the second year, and 3 died after the third year. At 5 years, 14 (8.3%) patients had been lost for follow-up. Group mean values for fatigue and the physical and psychosocial variables potentially related to fatigue at each assessment are shown in table 2.

[TABLE 2]

The severity of fatigue at baseline was high. The average score $\pm$ SD on the FSS was 5.1 ± 1.4 , and 80% of the patients had FSS fatigue scores greater than 4. The fatigue scores did not change significantly during the 5-year follow-up ($\beta = -.033$, $SE = .02$, $P = .097$) (see table 2). Patients with new muscle weakness and/or new muscle fatigue had higher fatigue scores ($\beta = 1.3$, $SE = 0.3$, $P = .001$), but the course of their fatigue during the 5-year follow-up did not differ from that of patients without new weakness and/or fatigue.

Over the course of the study, there was a significant decrease in physical functioning (SF-36) and walking capacity and a significant increase in comorbidity and extent of paresis. The most frequently reported comorbidities affected the following body systems: vascular (eg, hypertension) (26.8% of the patients at baseline and 32.2% at last assessment); skeletal, muscular, and skin (eg, arthrosis) (65.5% of the patients at baseline and 65.7% at last assessment); and endocrine and metabolic (eg, diabetes and hypothyroidism)

(19.1% of the patients at baseline and 35.6% at last assessment). The other potential variables did not change significantly over the 5-year period.

Univariate analysis revealed significant negative associations between fatigue and physical functioning ($\beta = -.022$, $P < .001$), walking capacity ($\beta = -.005$, $P < .024$), pain ($\beta = .016$, $P < .001$), and mental health ($\beta = -.012$, $P < .001$) (table 3). Univariate analysis also revealed significant positive associations between fatigue and all 3 coping styles, that is, task-oriented coping ($\beta = .037$, $P = .002$), emotional coping ($\beta = .043$, $P < .001$), and avoidance ($\beta = .027$, $P < .022$), as well as sleep disorders ($\beta = .007$, $P < .001$). There was no significant difference in the severity and course of fatigue in men and women.

Correlations between the variables that were significantly associated with fatigue were all below the cut-off value of 0.75 for multicollinearity. Hence, all variables with a univariate association were entered into the multivariable regression model for fatigue, revealing that physical functioning (standardized $\beta = -.305$, $P < .001$), pain (standardized $\beta = -.161$, $P < .001$), task-oriented coping (standardized $\beta = .155$, $P = .001$), mental health (standardized $\beta = .100$, $P = .008$), and sleep disorders (standardized $\beta = .084$, $P = .023$) were all independently associated with fatigue (table 4).

Physical functioning was strongly associated with walking capacity ($\beta = .332$, $SE = .035$, $P < .001$), which, in turn, was negatively associated with the extent of paresis ($\beta = 1.026$, $SE = .151$, $P < .001$)

DISCUSSION

This study demonstrates that fatigue is a common, severe, persistent, and multidimensional complaint in patients with LOSP. Confirming previous reports, fatigue in this study sample was severe, with an average FSS score of 5.1.^{2-4,6,24} Longitudinal studies of fatigue in polio survivors with late symptoms are scarce. In our study, fatigue remained high over a 5-year period. This result contrasts with findings in an earlier study of patients with PPS in which energy and fatigue, which were measured using different questionnaires than those used in this study, had improved significantly after 6 years compared to baseline.⁶ However, that study found a marked improvement during the first year of follow-up that was followed by gradual worsening of fatigue over the next 5 years. In our study sample, fatigue did not change over time, despite the fact that muscle strength and physical function gradually declined.¹³ On the other hand, the regular medical and rehabilitation care that was provided to the patients was not specifically aimed at reducing fatigue.

[TABLE 3]

We found that fatigue was associated with physical as well as psychosocial variables, namely physical functioning, pain, sleep disorders, mental health, and task-oriented coping. These results are inline with a smaller, cross-sectional study by Trojan et al⁷ that used different instruments. It is useful to consider how these variables might be connected with perceived fatigue.

Fatigue was associated with perceived restrictions in physical functioning. This could be explained by activities of daily living requiring greater effort of weakened muscles and reduced movement efficiency.^{10,24} Paresis was not a determinant of fatigue per se, but was associated with walking capacity, which in turn was associated with physical functioning. These associations are inline with reported relationships between walking capacity and extent of paresis and between walking capacity and physical functioning.^{13,25-27} This implies that polio survivors with more severe paresis are less capable of walking and perceive their physical functioning to be more demanding and fatiguing. It was interesting that fatigue remained unchanged while perceived physical functioning declined, as this may imply that the patients reduced their physical activity over time to avoid further increases in fatigue. This remains speculative, however, because we did not measure activity, which was found by Trojan⁷ to be significantly associated with fatigue.

A higher level of pain was associated with more fatigue, which is in agreement with earlier cross-sectional studies.^{7,28} Pain is a common and persistent problem in patients with LOSP and may cause people to diminish their activities, leading to deconditioning and hence fatigue.^{7,28} Pain could cause sleep disorders and thus result in more fatigue. However, pain was found to be a variable correlated with fatigue independent of sleep disorders, and this was also reported for fibromyalgia.

²⁹ Sleep disorders were positively associated with fatigue in our study sample, in agreement with the study by Trojan,⁷ as well as with observations in the general population.³⁰ Sleep disorders have been reported

more frequently by patients with LOSP than control subjects and have been related to a higher prevalence of obstructive sleep apnea syndrome and periodic limb movements in sleep.³¹⁻³³ Lower mental health scores on the SF-36 were associated with fatigue, which is in agreement with other studies of polio survivors, as well as with studies in the general population.^{4,10,34}

[TABLE 4]

Mental health in our cohort was comparable to that in a Dutch reference population, providing corroboration that psychologic problems and psychiatric diagnoses (eg, depression) are not found more frequently in polio survivors with late symptoms.^{10,35,36} A task-oriented coping style correlated with higher levels of fatigue. Task-oriented coping, also known as problem-focused coping, consists of actively resolving a problem by acting on the environment or oneself.³⁷ Emotional coping is the adaptation of emotional reactions associated with the problem; it is more dominant in situations in which illness-related problems cannot be resolved.^{37,38} As fatigue in patients with LOSP cannot be cured, a higher use of emotional coping is expected. Polio survivors have been found to use problem-focused coping more often than emotional coping.^{4,38} The higher use of task-oriented coping may be due to the strong motivation of patients with LOSP to be self-sufficient, to actively solve problems, and, often, to push themselves beyond their physical abilities to achieve their goals.^{39,40} Thus, patients with LOSP may persist in their behaviors despite decreasing physical functioning at the cost of increased fatigue. Both emotional and task-oriented coping were associated with fatigue in this study. In the multivariable model, however, emotional coping was not an independent factor. That may be because of an overlap in the concepts of emotional coping and mental health.

Study Limitations

This study also has some limitations. Associations between fatigue and the different variables were investigated with GEE.

However, this technique cannot answer the question of whether relationships are causal. Causality and treatment amenability need to be investigated in future studies.

We studied a limited number of possible variables for fatigue.

For example, we did not include treatments patients received as a variable. During the course of the study, 14 patients (8.3%) participated in a multidisciplinary rehabilitation program because of PPS, which may have affected their fatigue.

Comorbidity was quantified using the CIRS with a cumulative count of prevalent comorbid conditions in 13 body systems.

This assumes that all comorbidities have an equal effect on outcome in terms of magnitude and direction and does not take into account the differential effects of disease severity.

This may explain our finding that comorbidity was not associated with fatigue.

Patients who reported new muscle weakness or muscle fatigue at baseline did not show a different course of fatigue than the patients without new muscle weakness or fatigue. This observation is in line with an earlier report from CARPA that the course of disability and muscle strength did not differ between patients with and without new muscle weakness or fatigue.¹³ It is therefore likely that the results of this study are also applicable to patients with PPS.

Despite these limitations the strengths of our study are its longitudinal design, which included 5 assessments over a 5-year period, the large cohort size (N=168), the wide age range (45-81y), and the low dropout rate (7.7% over 5y).

Clinical Implications

This study identified potentially modifiable variables associated with fatigue: physical functioning, pain, sleep disorders, mental health, and task-oriented coping. These variables could provide opportunities for treatment. Fatigue in polio survivors with LOSP is a multidimensional problem, and treatment should be multidisciplinary with attention to both physical and psychologic determinants, including pain management, exercise therapy, and cognitive behavioral therapy. Although not tested in patients with LOSP, the effectiveness of cognitive behavioral therapy in reducing fatigue has been demonstrated in

chronic fatigue syndrome, fatigued cancer survivors, and multiple sclerosis.^{11,41,42} A recent pilot study on the effectiveness of a multidisciplinary rehabilitation program for PPS showed prolonged benefits, such as decreased fatigue.⁴³ More research on multidisciplinary treatment protocols targeting the variables associated with fatigue is still needed. The efficacy of 2 interventions on fatigue (ie, physical therapy and cognitive behavioral therapy) is currently being evaluated in an ongoing multicenter randomized trial in PPS patients.⁴⁴

CONCLUSIONS

Fatigue in patients with LOSP is a severe and persistent problem that correlates with physical and psychologic variables.

Some of these variables can potentially be modified, which may provide an opportunity for treating fatigue. Further study is needed to investigate the efficacy of treatment directed at modifying these physical and psychologic determinants.

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TABLES

List of Abbreviations

CARPA	Comorbidity and Aging effects in Rehabilitation Patients on Activities
CIRS	Cumulative Illness Rating Scale
FSS	Fatigue Severity Scale
GEE	generalized estimating equations
LOSP	late-onset sequelae of poliomyelitis
PPS	postpolio syndrome
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey

Table 1: Patient Characteristics

Characteristics at Baseline	(N=168)
Sex (men/women)	67/101
Age, y (mean $\pm$ SD)	59 $\pm$ 8
Range, y	45–81
Marital status (n married [%])	121 (72)
Time since onset of polio, y (mean $\pm$ SD)	55 $\pm$ 8
Body parts affected by polio (n [%])	
Right arm	28 (17)
Left arm	31 (39)
Back and abdomen	22 (13)
Right leg	106 (63)
Left leg	107 (64)
New neuromuscular symptoms (n [%])	147 (88)
New muscle weakness (n [%])	138 (82)
New muscle fatigue (n [%])	114 (68)

Table 2: Descriptive Data for Independent and Dependent Variables

Characteristics Fatigue and Potential Determinants	Baseline	T1	T2	T3	T4	Course β (SE)
Fatigue (FSS) (1–7)	5.1±1.4 (167)	5.2±1.4 (160)	5.2±1.4 (160)	5.1±1.4 (156)	5.0±1.5 (148)	.033 (.020) $P=.097$
SF-36 physical functioning (0–100)	39±24 (167)	38±24 (159)	37±24 (155)	35±24 (149)	36±25 (149)	–0.689 (0.262) $P=.009$
SF-36 bodily pain (0–100)	56±22 (168)	58±24 (162)	58±23 (160)	56±24 (158)	56±22 (149)	–.264 (.322) $P=.413$
Extent of paresis* (0–130)	109±20 (168)	109±18 (157)	109±17 (154)	107±20 (147)	106±17 (149)	–.722 (.081) $P<.001$
Walking capacity (m)	126±34 (152)	124±33 (144)	127±34 (139)	127±34 (131)	124±33 (113)	–.864 (.042) $P=.008$
Comorbidity (CIRS total score) (0–52)	6.5±3.7 (168)	6.9±3.9 (158)	7.0±3.8 (157)	7.7±4.0 (155)	8.1±4.2 (149)	.299 (.42) $P<.001$
Sleep disorders (NHP sleep) (0–100)	22±30 (168)	24±29 (160)	24±30 (162)	25±30 (153)	25±29 (149)	.442 (.408) $P=.279$
SF-36 mental health (0–100)	75±17 (168)	72±19 (161)	75±18 (160)	75±17 (155)	76±19 (149)	.315 (.262) $P=.229$
Task-oriented coping style (0–35)	25±6 (167)	25±6 (160)	24±7 (161)	25±6 (158)	25±6 (147)	.079 (.088) $P=.372$
Emotional coping style (0–35)	17±6 (167)	17±6 (160)	16±6 (161)	17±6 (158)	16±6 (147)	–.0150 (.080) $P=.06$
Avoidance coping style (0–35)	14±6 (167)	15±6 (160)	15±6 (161)	15±6 (158)	14±6 (147)	–.043 (.087) $P=.622$
Social support (0–60)	55±8 (166)	56±8 (160)	56±8 (162)	55±9 (156)	56±7 (149)	.191 (.098) $P=.051$

NOTE. Values are mean $\pm$ SD (n) or as otherwise noted.

Abbreviations: NHP, Nottingham Health Profile; T1, 1-year follow-up; T2, 2-year follow-up; T3, 3-year follow-up; T4, 5-year follow-up.

*Extent of paresis: score range 0 to 130 with 130 as full muscle capacity in all of the 26 muscle groups.

Table 3: Correlations Among All Dependent and Independent Variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12
1. Fatigue	1											
2. Physical functioning	–.40 [†]	1										
3. Pain	–.41 [†]	.33 [†]	1									
4. Extent of paresis	–.09	.49 [†]	.19*	1								
5. Walking capacity	–.15*	.69 [†]	.28*	.62 [†]	1							
6. Comorbidity	.12	–.29 [†]	–.28 [†]	–.06 [†]	–.26 [†]	1						
7. Sleep disorders	.19 [†]	–.10	–.24 [†]	–.04	–.09	.22*	1					
8. Mental health	–.26 [†]	.04	.25 [†]	–.11	.04	–.13	–.24 [†]	1				
9. Task-oriented coping	.19 [†]	.06	–.07	–.03	.08	–.11	–.05	–.04	1			
10. Emotional coping	.28 [†]	–.10	–.23 [†]	–.05	–.08	.11	.20 [†]	–.46 [†]	.19 [†]	1		
11. Avoidance coping	.09*	–.06	–.07	–.05	–.07	–.11	.08	–.10	.25 [†]	.25 [†]	1	
12. Social support	.11	.11	–.05	–.02	–.05	–.10	–.17	.28 [†]	.00	.21 [†]	.18*	1

* $P<.05$; [†] $P<.001$.

Table 4: Linear Longitudinal Multivariable Model

Determinant	Standardized β	P
Physical functioning	–0.305	<.001
Pain	–0.161	<.001
Task-oriented coping	0.155	<.001
Mental health	0.100	.008
Sleep disorders	0.084	.023