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**ORIGINAL REPORT**

# IMMUNOGLOBULIN TREATMENT IN POST-POLIO SYNDROME: IDENTIFICATION OF RESPONDERS AND NON-RESPONDERS

Gunilla Östlund, PhD, Lisbet Broman, CLS, Lars Werhagen, MD, PhD and Kristian Borg, MD, PhD

*From the Division of Rehabilitation Medicine, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden*

***Objective:*** **To define and characterize responders and non-responders in a group of 124 patients with post-polio syndrome who received a single treatment with intravenous immunoglobulin.**

***Design:*** **Open trial, prospective follow-up study.**

***Methods:*** **Clinical examination and data from medical records. Short Form 36 (SF-36), Physical Activity Scale for the Elderly (PASE) and visual analogue scale (VAS) measured quality of life, physical activity and intensity of pain, respectively. Data were obtained before treatment and at 6-month follow-up.**

***Results:*** **Two responder groups were identified with the outcome SF-36 Vitality and 3 with Bodily pain, respectively. Forty-five percent were positive-responders, identified before treatment by reduced physical function, muscle atrophy in the lower extremities, higher levels of fatigue and pain, and a VAS pain score above 20. Negative-responders were identified by good physical function and mental health, lesser muscle atrophy in the lower extremities, and low levels of fatigue and pain.**

***Conclusion:*** **Intravenous immunoglobulin is a biological intervention, and therefore it is important to be able to identify responders and non-responders. In order to maximize a positive outcome it is suggested that patients with a high level of fatigue and/or pain and reduced physical function are selected.**

*Key words:* post-polio syndrome; IVIG; responders; non-responders; fatigue; pain; VAS score; physical function.

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*Correspondence address: Gunilla Östlund, Department of Rehabilitation Medicine, Danderyd University Hospital, Building 39, 3rd Floor, SE-182 88 Stockholm, Sweden. E-mail: Gunilla.Ostlund@ki.se, gunilla.ostlund@ds.se*

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## INTRODUCTION

Acute poliomyelitis infection may affect the anterior horn cells (1) leaving prior polio patients with residual muscle weakness. In some cases a late increase in symptoms or new symptoms may occur; a condition known as post-polio syndrome (PPS) (2).

The most common symptoms in PPS are muscle weakness, fatigue and pain in the muscles and joints (3–8). Physical fatigue is the dominant type (9), but general fatigue, described as a flu-like exhaustion worsened by physical activity, is also experienced (5). The dominant pain in patients with PPS is of nociceptive character (10). In a study by Vasiliades et al. (11) patients with PPS with muscle pain had a higher level of fatigue and a lower level of quality of life (QoL) than those without pain.

The main treatment options for patients with PPS are physiotherapy, muscle training and energy conservation techniques (12). PPS-related pain is treated by means of medication, bracing and weight reduction (8). An inflammatory process in the central nervous system (CNS) and peripheral blood has been described (13–16). This process has been shown to be down-modulated by means of intravenous immunoglobulin (IVIG), followed by a clinical improvement in vitality, muscle strength (17), pain (15) and mental well-being (18).

IVIG is an important treatment option for autoimmune and acute inflammatory conditions (19, 20) as well as for different pain conditions (21) that involve immune changes in the peripheral tissues or CNS (21). However, IVIG may act differently between different pain syndromes and between individuals within the same condition, i.e. there are responders and non-responders (22).

A study by Werhagen & Borg (10) showed that pain was decreased after IVIG treatment in younger patients with PPS, in those who had polio before the age of 10 years, and in those with pronounced paresis. In a study by Östlund et al. (23) improvements in vitality and pain were seen in patients with a visual analogue scale (VAS) score of 20 or more, in those under 65 years of age, and in those who had paresis in the lower extremities and had no concomitant disorders. These findings (10, 23) are in agreement with the finding in the study by Gonzales et al. (24), in which a decrease in pain was seen after IVIG treatment in patients with PPS with a pain intensity score greater than 20 according to a VAS before treatment. The present study is a further development of the study by Östlund et al. (23), in which an increased level of Short Form-36 (SF-36) scales Vitality and Bodily pain were seen 6 months after IVIG treatment, indicating that these outcome variables should be studied further. Parameters of value for a future characterization of responder groups were also identified (23).

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The aim of this study was therefore to define and characterize responders and non-responders to IVIG treatment in a PPS population, using SF-36 Vitality and Bodily pain as outcome; and to characterize these groups pre-treatment using demographic and medical background, pain, physical activity and QoL variables.

## METHODS

### *Participants*

A total of 124 patients from the post-polio out-patient clinic at Danderyd University Hospital, Stockholm, Sweden were included in the study. All patients were diagnosed with PPS according to the March of Dimes (2) criteria. Inclusion criteria were: increased muscle fatigue and/or muscle weakness, or an increase in general fatigue during recent years. Exclusion criteria were: low levels of IgA, decreased peripheral blood circulation, cardiovascular disorders, including atrial fibrillation, and previous treatment with IVIG or other immune modulators. In order to be included in the present study the patients also had to answer an inventory both before treatment and at 6-month follow-up. The patients were treated with a total of 90 g IVIG (Xepol, Grifols, Barcelona, Spain) over a period of 3 consecutive days. The treatments were given between November 2005 and May 2012.

### *Background variables*

All patients participating in the present study were clinically evaluated by 1 of the authors (LW or KB). All additional demographic and medical background variables were retrieved from medical files. Included in the present study are demographic and medical background data predicting a significant change in SF-36 Vitality and Bodily pain 6 months after IVIG treatment, as identified in the study by Östlund et al. (23). Some data were missing, but this was considered not to affect the outcome of the present study. Demographic and medical background variables were dichotomized. Age was divided into younger or older than 65 years, and age at acute polio onset into younger or older than 10 years of age. In the study by Gonzales et al. (24) pain intensity above 20 according to the VAS, was identified as significant pain. In this study pain intensity according to the VAS was dichotomized into a score of 0–19 mm and 20–100 mm. With the exception of nationality and civil status (Table I), the demographic and medical background variables were divided into yes and no.

### *Inventories and scales*

*SF-36.* The health-related QoL inventory SF-36 comprises 36 questions on the following 8 scales: Physical function, Role-Physical, Bodily pain, General health, Vitality, Social function, Role emotional, and Mental health. A score of 0–100 is calculated for each scale, and better QoL is indicated by a higher score. The physical compound score (PCS) includes Physical function, Role physical, and Bodily pain. The mental compound score (MCS) includes Mental health, Role emotional, and Social function. The scales Vitality, General health, and Social function correlate with both PCS and MCS (25). SF-36 includes a question calculated outside the inventory about the patient's concept of their general health one year previously. The 5 possible answers are: much worse, somewhat worse, the same, somewhat better, and much better health compared with one year previously (26–28). For the purpose of this paper these were combined into 3 possible answers: much/somewhat worse, the same, and somewhat/much better.

*Physical Activity for the Elderly (PASE).* PASE is a 10-question instrument especially developed for persons over 65 years of age in order to measure physical activity over a period of one week. Four questions concern paid or unpaid work and are recorded in hours/week. Six questions cover participation in leisure activities and are recorded as never/seldom (1–2 days a week), sometimes (3–4 days a week), and often (5–7 days a week). Duration is categorized as less than 1, 1–2, 2–4, and >4 h. Scores range from a minimum value of zero to a maximum value of 400 and are calculated from weight and frequency values. More physical activity is indicated by a higher total score (29).

*Pain according to visual analogue scale (VAS).* In order to assess pain intensity a 100-mm VAS scale was used, where zero represents no pain at all and 100 mm the worst imaginable pain (30).

*Baseline and follow-up.* A standardized inventory composed of SF-36, PASE and VAS measuring pain intensity was given to the participants when they had been included in the IVIG treatment study. The inventory was answered by the participants before the first IVIG treatment and at the first follow-up after a mean of 6 months (standard deviation (SD) 3).

### *Ethics*

The study and all procedures were approved by the Ethical Review Board in Stockholm (Dnr. Protocol 2010/1.3), Sweden, and were conducted in accordance with the principles of the Declaration of Helsinki of 1975.

### *Outcome variables*

Pain in muscles and/or joints and fatigue are 2 of the most common symptoms in PPS (5–8). In a study by Östlund et al. (23), the SF-36 scales Vitality and Bodily pain were statistically increased 6 months after IVIG treatment in a sample of 113 patients with PPS. In the study by Östlund et al. (9) the Multi Fatigue Inventory 20 (MFI20) variable General fatigue accounted for 69% of the variation in the SF-36 scale Vitality in patients with PPS, indicating that SF-36 Vitality is assessing fatigue in this patient group. SF-36 Vitality and Bodily pain were therefore considered as suitable outcome variables after IVIG treatment in the present study. SF-36 Vitality is defined as how much you have felt strong and alert, full of energy or worn out or tired during the last 4 weeks. SF-36 Bodily pain is defined as how much pain was felt and how much this pain interfered with work during the last 4 weeks (28).

### *Power*

The sample power was calculated according to the SF-36 Swedish manual and interpretation guide, in which study design, effect size and sample size are taken into consideration with a significance level of $p \leq 0.05$. The purpose of the present study was to detect differences within a single group of 124 participants. To detect a moderate difference with a difference of 10 points within a single group the recommended sample size for the SF-36 scale Vitality is 28 individuals and for Bodily pain 36 individuals (27, 28). The sample size in the present study was therefore considered sufficiently large.

### *Responder groups for SF-36 Vitality and Bodily pain*

An increase of 11 points or more at 6-month follow-up on SF-36: Vitality and Bodily pain compared with before treatment defined a positive-responder group. No change, or a change of less than 11 points increase or decrease, was defined as non-responders. Negative-responders were defined as a decrease of 11 points or more.

### *Statistical analysis*

All statistical analysis was carried out using IBM SPSS Statistics 20.0.

Demographics and frequencies were determined for all variables included in the study before treatment in positive-, non- and negative-responder groups. In the first analysis Mann-Whitney tests were used for comparisons of SF-36 variables, PASE and pain according to the VAS scale between groups before treatment. In the second analysis $\chi^2$ was used for a comparison of dichotomized demographic and medical background variables between groups before treatment. In both analyses the significance level was set at $p < 0.05$ (27, 28).

## RESULTS

### *Responder groups*

With Vitality as outcome 38% of the participants who had received IVIG were positive-responders, 45% non-responders, and 17% negative-responders. With Bodily pain as outcome 29% were positive-responders, 56% non-responders, and 15% negative-responders. Seventeen percent of participants had a positive response for both Vitality and Bodily pain, 17% had a positive response only with Vitality and a non-response for Bodily pain. Twelve percent had a positive response for Bodily pain and a non-response for Vitality. In total 46% of the participants were positive-responders for one or both of the outcome variables.

### *SF-36 Vitality and Bodily pain as outcome*

In all responder groups, independent of outcome, the proportions of women and men were almost equal, the majority had had acute poliomyelitis before the age of 10 years, were married or co-habiting, were of Swedish origin, and were not participating in the working market (Table I).

### *SF-36 Vitality as outcome*

Descriptive and frequency information about demographic variables in positive-, non-, and negative responder groups are presented in Table I. Fifty-two percent of the participants in the positive-responder group, 44% in the non-responder group, and 38% in the negative-responder groups were under 65 years of age. When answering the question included in the SF-36 inventory regarding change in health compared with 1 year previously the majority in the positive- and non-responder groups considered their health to be "much/somewhat worse". None of the patients in the negative-responder group considered their health to be "much/somewhat worse" than one year previously.

Table II shows group differences and descriptive and frequency information for medical background variables. No significant differences between the 3 groups were seen for PPS syndrome without co-morbidity and paresis. Seventy percent of the non-responder group had a VAS-pain intensity score between 20 and 100 mm, which was significantly more ($p = 0.019$) than the 40% in the negative-responder group. Significantly more (84%, $p = 0.042$) in the positive-responder group had muscle weakness and atrophies only in the lower extremities, compared with 63% in the non-responder group.

Table III shows group differences in the SF-36 and PASE. In the positive-responder group significantly lower SF-36 scores were seen for Bodily pain ($p = 0.045$), Vitality ($p = 0.0001$) and MCS ($p = 0.033$) compared with negative-responders.

In the non-responder group Vitality ($p = 0.017$), Role emotional ($p = 0.020$), Mental health ($p = 0.028$), and MCS

Table I. *Demographic variables for positive-, non- and negative-responders before intravenous immunoglobulin (IVIG) treatment with Short Form 36 (SF-36) Vitality or Bodily pain as outcome*

| | Vitality | | | | | | Bodily pain | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Positive-responders $n=46$ | | Non-responders $n=54$ | | Negative-responders $n=21$ | | Positive-responders $n=36$ | | Non-responders $n=69$ | | Negative-responders $n=18$ | |
| Variable | *n* | *n* (%) | *n* | *n* (%) | *n* | *n* (%) | *n* | *n* (%) | *n* | *n* (%) | *n* | *n* (%) |
| Age | | | | | | | | | | | | |
| <65 years | 46 | 24 (52) | 54 | 24 (44) | 21 | 8 (38) | 36 | 19 (53) | 69 | 31 (45) | 18 | 7 (39) |
| >65 years | | 22 (48) | | 30 (56) | | 13 (62) | | 17 (47) | | 38 (55) | | 11 (61) |
| Age at polio onset | | | | | | | | | | | | |
| <10 years | 43 | 31 (72) | 53 | 33 (62) | 20 | 14 (70) | 34 | 21 (62) | 66 | 47 (71) | 18 | 11 (61) |
| >10 years | | 12 (28) | | 20 (38) | | 6 (30) | | 13 (38) | | 19 (29) | | 7 (39) |
| Sex | | | | | | | | | | | | |
| Female | 46 | 22 (48) | 54 | 25 (46) | 21 | 11 (52) | 36 | 16 (44) | 69 | 34 (49) | 18 | 8 (44) |
| Male | | 24 (52) | | 29 (54) | | 10 (48) | | 20 (56) | | 35 (51) | | 10 (56) |
| Civil status | | | | | | | | | | | | |
| Married/cohabiting | 39 | 28 (72) | 46 | 24 (52) | 18 | 10 (55) | 32 | 21 (66) | 56 | 35 (63) | 16 | 7 (44) |
| Single | | 3 (8) | | 5 (11) | | 5 (28) | | 2 (6) | | 4 (7) | | 6 (34) |
| Other | | 8 (20) | | 17 (37) | | 3 (17) | | 9 (28) | | 17 (30) | | 3 (19) |
| Nationality | | | | | | | | | | | | |
| Swedish | 42 | 40 (95) | 52 | 46 (88) | 21 | 18 (86) | 33 | 31 (94) | 66 | 60 (91) | 18 | 15 (83) |
| European | | 1 (2) | | 2 (4) | | 1 (5) | | 1 (3) | | 2 (3) | | 1 (6) |
| Non-European | | 1 (2) | | 4 (8) | | 2 (9) | | 1 (3) | | 4 (6) | | 2 (11) |
| Work | | | | | | | | | | | | |
| Working | 43 | 16 (37) | 51 | 15 (29) | 20 | 6 (30) | 34 | 13 (38) | 64 | 21 (33) | 18 | 3 (17) |
| Not working | | 27 (63) | | 36 (71) | | 14 (70) | | 21 (62) | | 43 (67) | | 15 (83) |
| Change of health before treatment | | | | | | | | | | | | |
| Much/somewhat worse than | 43 | | 49 | | 20 | | 34 | | 64 | | 16 | |
| one year ago | | 28 (65) | | 31 (63) | | 0 (0) | | 20 (57) | | 44 (69) | | 11 (69) |
| The same as one year ago | | 11 (26) | | 13 (27) | | | | | | | | |
| Somewhat/much better than | | | | | | 14 (70) | | 12 (35) | | 15 (23) | | 3 (19) |
| one year ago | | 4 (9) | | 5 (10) | | 6 (30) | | 2 (6) | | 5 (8) | | 2 (13) |

Table II. *Between-group comparisons for medical background variables in positive-, non- and negative-responders before intravenous immunoglobulin treatment with Short Form 36 (SF-36) Vitality as outcome*

| Variable | Positive-responders $n=46$ | | Non-responders $n=54$ | | Negative-responders $n=21$ | | Positive- vs negative-responders $p$-value | Positive- vs non-responders $p$-value | Non- vs negative-responders $p$-value |
|---|---|---|---|---|---|---|---|---|---|
| | *n* | *n* (%) | *n* | *n* (%) | *n* | *n* (%) | | | |
| Only PPS | 46 | | 54 | | 21 | | 0.905 | 0.806 | 0.753 |
| Yes | | 27 (59) | | 33 (61) | | 12 (57) | | | |
| No | | 19 (41) | | 21 (39) | | 9 (43) | | | |
| VAS-pain score | 46 | | 53 | | 20 | | 0.057 | 0.626 | 0.019 |
| 0–19 | | 16 (35) | | 16 (30) | | 12 (60) | | | |
| 20–100 | | 30 (65) | | 37 (70) | | 8 (40) | | | |
| Paresis | 41 | | 48 | | 20 | | 0.176 | 0.079 | 0.865 |
| Yes | | 39 (95) | | 40 (83) | | 17 (85) | | | |
| No | | 2 (5) | | 8 (17) | | 3 (15) | | | |
| Only upper extremities | 41 | | 48 | | 20 | | 0.511 | 0.506 | 0.895 |
| Yes | | 11 (27) | | 16 (33) | | 7 (35) | | | |
| No | | 30 (73) | | 32 (67) | | 13 (65) | | | |
| Only lower extremities | 41 | | 48 | | 20 | | 0.115 | 0.153 | 0.706 |
| Yes | | 37 (90) | | 38 (79) | | 15 (75) | | | |
| No | | 4 (10) | | 10 (21) | | 5 (25) | | | |
| Atrophies | 43 | | 50 | | 20 | | 0.170 | 0.184 | 0.604 |
| Yes | | 37 (86) | | 38 (76) | | 14 (70) | | | |
| No | | 5 (12) | | 12 (24) | | 6 (30) | | | |
| Only upper extremities | 38 | | 45 | | 19 | | 0.787 | 0.981 | 0.796 |
| Yes | | 5 (13) | | 5 (11) | | 3 (16) | | | |
| No | | 33 (87) | | 33 (73) | | 16 (84) | | | |
| Only lower extremities | 38 | | 45 | | 19 | | 0.074 | 0.042 | 0.922 |
| Yes | | 32 (84) | | 29 (64) | | 12 (63) | | | |
| No | | 6 (16) | | 16 (36) | | 7 (37) | | | |

Significance level at $p<0.05$.
PPS: post-polio syndrome; VAS: visual analogue scale.

($p=0.045$) were significantly lower compared with the negative-responders. There were no significant differences between positive-responders and non-responders.

*SF-36 Bodily pain as outcome*

Descriptive and frequency information about demographic variables in positive-, non- and negative responders are shown in Table I. Fifty-three percent in the positive-responder, 45% in the non-responder, and 39% in the negative-responder group were under 65 years of age. The majority in the positive- (57%) and the non- and negative-responder groups (69%), considered their health as "much/somewhat worse" than one year ago.

Table IV shows group differences and descriptive and frequency information for medical background variables. No significant differences were seen between the 3 groups for PPS syndrome without co-morbidities, paresis and atrophies. Seventy-one percent of subjects in the positive-responder, and 65% in the non-responder group had a VAS score between 20 and 100 mm, which was significantly more than the 39% in the negative-responder group.

Table IV shows group differences for SF-36, PASE and pain according to the VAS. Significantly lower scores for Bodily pain ($p=0.0001$), Vitality ($p=0.046$) and PASE ($p=0.053$) were seen in the positive-responder group compared with negative-responders. Significantly lower scores were also seen in the positive-responder group for Bodily pain ($p=0.014$) compared with non-responders. Bodily pain scores were also significantly lower ($p=0.030$) in non-responders compared with negative-responders.

## DISCUSSION

Two significantly different responder groups were identified with Vitality as outcome, and 3 significantly different groups with Bodily pain as outcome. Forty-six percent of participants had a positive response with Vitality and/or Bodily pain as outcome. Positive-responders were identified by a higher level of fatigue and pain, scoring 20 or higher on a VAS pain intensity scale, and muscle weakness and atrophy in the lower extremities. Negative-responders were identified by a low level of fatigue and pain, good mental health, good physical function and, to a lesser degree, muscle weakness and atrophy in the lower extremities.

IVIG is a current treatment option in several conditions (19, 20) and has been used in chronic pain (21, 22). The problem of identifying responders and non-responders is therefore not unique to PPS. Since IVIG is a biological treatment that may result in side-effects, it is of importance to identify and characterize patients who have a favourable effect.

In patients with PPS there are several indications of an ongoing inflammatory process. One is the increased level of cytokines found both in cerebrospinal fluid (CSF) and in peripheral blood (13–16), a process dampened by IVIG treatment (14). In the

Table III. *Between-group comparison for Short Form 36 (SF-36) and Physical Activity Scale for the Elderly (PASE) in positive-, non- and negative-responders before intravenous immunoglobulin treatment with SF-36 Vitality or Bodily pain as outcome*

| | | Positive-responders | | Non-responders | | Negative-responders | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | *n* | Before Mean (SD | *n* | Before Mean (SD) | *n* | Before Mean (SD) | Positive vs negative *p*-value | Positive vs non *p*-value | Non vs negative *p*-value |
| *Vitality* | | | | | | | | | |
| Short Form 36 | | *n*=46 | | *n*=54 | | *n*=21 | | | |
| Physical function | 45 | 41 (23) | 53 | 37 (21) | 20 | 35 (24) | 0.301 | 0.476 | 0.476 |
| Role physical | 44 | 26 (33) | 54 | 32 (38) | 20 | 45 (41) | 0.091 | 0.527 | 0.238 |
| Bodily pain | 46 | 47 (24) | 54 | 48 (25) | 21 | 57 (22) | 0.045 | 0.848 | 0.082 |
| General health | 46 | 49 (23) | 53 | 48 (22) | 20 | 52 (20) | 0.581 | 0.808 | 0.399 |
| Vitality | 46 | 34 (19) | 54 | 41 (24) | 21 | 54 (17) | 0.000 | 0.173 | 0.017 |
| Social function | 46 | 67 (25) | 54 | 66 (27) | 21 | 70 (27) | 0.696 | 0.850 | 0.542 |
| Role emotional | 43 | 57 (41) | 53 | 50 (44) | 20 | 77 (38) | 0.068 | 0.407 | 0.020 |
| Mental health | 46 | 70 (20) | 54 | 68 (21) | 21 | 80 (14) | 0.076 | 0.700 | 0.028 |
| PCS | 41 | 29 (9) | 51 | 30 (8) | 19 | 29 (9) | 0.956 | 0.854 | 0.817 |
| MCS | 41 | 45 (12) | 51 | 44 (14) | 19 | 52 (9) | 0.033 | 0.928 | 0.045 |
| PASE | 37 | 96 (53) | 46 | 92 (51) | 19 | 98 (82) | 0.066 | 0.702 | 0.120 |
| *Bodily pain* | | | | | | | | | |
| Short Form 36 | | *n*=36 | | *n*=69 | | *n*=18 | | | |
| Physical function | 35 | 37 (22) | 68 | 39 (23) | 17 | 39 (19) | 0.653 | 0.704 | 0.952 |
| Role physical | 34 | 25 (31) | 69 | 33 (38) | 17 | 40 (40) | 0.210 | 0.575 | 0.383 |
| Bodily pain | 36 | 38 (18) | 69 | 51 (25) | 18 | 62 (23) | 0.000 | 0.014 | 0.030 |
| General health | 35 | 48 (23) | 67 | 48 (22) | 17 | 56 (16) | 0.226 | 0.949 | 0.188 |
| Vitality | 36 | 37 (19) | 68 | 40 (22) | 18 | 49 (25) | 0.046 | 0.555 | 0.132 |
| Social function | 36 | 67 (24) | 69 | 65 (28) | 18 | 72 (25) | 0.403 | 0.787 | 0.324 |
| Role emotional | 33 | 60 (42) | 68 | 54 (43) | 17 | 65 (43) | 0.677 | 0.529 | 0.342 |
| Mental health | 36 | 68 (20) | 68 | 70 (20) | 18 | 77 (17) | 0.101 | 0.679 | 0.117 |
| PCS | 30 | 28 (7) | 65 | 30 (9) | 16 | 32 (8) | 0.059 | 0.256 | 0.236 |
| MCS | 30 | 46 (11) | 65 | 45 (14) | 16 | 49 (14) | 0.268 | 0.816 | 0.349 |
| PASE | 33 | 99 (66) | 57 | 90 (52) | 13 | 101 (65) | 0.053 | 0.132 | 0.217 |

Significance level at $p < 0.05$.

PCS: physical compound score; MCS: mental compound score; SD: standard deviation.

study by Gonzales et al. (17) Vitality as well as muscle strength was increased in the treatment group compared with placebo one year after IVIG treatment. In the study by Bertolasi et al. (18) patients with PPS treated with IVIG had a significant increase in mental well-being compared with placebo at a 2-month follow-up, and in the study by Farbu et al. (15) pain was significant reduced after IVIG treatment in a follow-up. One aim of the current study was to identify responder groups. However the difference of 10 points in SF-36 Vitality chosen in this study seems not to be sufficient to identify a difference in fatigue between positive- and non-responders. The result is in accordance with the patient's own subjective evaluation of their general health one year previously, in which two-thirds of patients, both in the positive- and non-responder groups, considered their health to be declining, whereas none of the negative-responders considered their health as worse. There is obviously a discrepancy between the increase in symptoms as reported by the patients when examined clinically and their report in the SF-36. This may indicate that negative-responders do not have a progressive course, and this should be taken into consideration in further studies. With Bodily pain as outcome the 10-point difference was sufficient to identify a significant difference between positive-, non- and negative-responders.

In addition, as with different outcomes, it is either mental or physical QoL factors that constitute the difference between positive- and negative-responders before IVIG treatment. With Vitality as outcome, positive-responders had significantly lower scores on mental variables, i.e. MCS, than did negative-responders. With Bodily pain as outcome, the positive-responders had lower scores on physical variables, i.e. PCS, than negative-responders. This is in accordance with the findings of Werhagen & Borg (10), that patients with PPS reporting pain had a lower PCS score than patients with PPS reporting no pain. These findings should be investigated further.

With Vitality as outcome significantly more positive- and non-responders had a VAS-score above 20 compared with negative-responders. With Bodily pain as outcome significantly more positive-responders had pain according to the VAS scale above 20 compared with negative-responders. This indicates that the cut-off of 20 mm for VAS pain may be sufficient to exclude negative-responders. It also indicates that positive-responders and non-responders with Vitality as outcome act as a single group and that positive-responders with Bodily pain as outcome are a distinct group different from non-responders. From these data it seems that a high pain intensity measured by VAS indicates a positive response to IVIG. This is in accordance with the results of the studies by Östlund et al. (23) and Werhagen & Borg (10). The lower level of fatigue and pain in negative-responders, indicates that an absence of these symptoms could be a valuable indicator in identifying

Table IV. *Between-group comparisons for medical background variables in positive-, non- and negative-responders before intravenous immunoglobulin treatment with Short Form 36 (SF-36) Bodily pain as outcome*

| Variable | Positive-responders $n=36$ | | Non-responders $n=69$ | | Negative-responders $n=18$ | | Positive- vs negative-responders $p$-value | Positive- vs non-responders $p$-value | Non- vs negative-responders $p$-value |
|---|---|---|---|---|---|---|---|---|---|
| | $n$ | $n$ (%) | $n$ | $n$ (%) | $n$ | $n$ (%) | | | |
| Only PPS | 36 | | 69 | | 18 | | 0.697 | 0.599 | 0.985 |
| Yes | | 16 (44) | | 42 (61) | | 11 (61) | | | |
| No | | 20 (56) | | 27 (39) | | 7 (39) | | | |
| VAS-pain score | 35 | | 68 | | 18 | | 0.022 | 0.492 | 0.047 |
| 0–19 | | 10 (29) | | 24 (35) | | 11 (61) | | | |
| 20–100 | | 25 (71) | | 44 (65) | | 7 (39) | | | |
| Paresis | 33 | | 62 | | 16 | | 0.962 | 0.142 | 0.209 |
| Yes | | 27 (82) | | 57(92) | | 13 (81) | | | |
| No | | 6 (18) | | 5 (8) | | 3 (19) | | | |
| Only upper extremities | 33 | | 62 | | 16 | | 0.057 | 0.106 | 0.463 |
| Yes | | 6 (18) | | 21 (34) | | 7 (44) | | | |
| No | | 27 (82) | | 41 (66) | | 9 (56) | | | |
| Only lower extremities | 33 | | 62 | | 16 | | 0.962 | 0.958 | 0.925 |
| Yes | | 27 (82) | | 51 (82) | | 13 (81) | | | |
| No | | 6 (18) | | 11 (18) | | 3 (19) | | | |
| Atrophies | 34 | | 62 | | 18 | | 0.313 | 0.316 | 0.860 |
| Yes | | 24 (71) | | 51 (82) | | 15 (83) | | | |
| No | | 10 (29) | | 11 (18) | | 3 (17) | | | |
| Only upper extremities | 31 | | 57 | | 16 | | 0.296 | 0.737 | 0.137 |
| Yes | | 4 (13) | | 51 (89) | | 4 (25) | | | |
| No | | 27 (87) | | 6 (11) | | 12 (75) | | | |
| Only lower extremities | 31 | | 57 | | 16 | | | | |
| Yes | | 20 (65) | | 43 (75) | | 11 (69) | 0.772 | 0.278 | 0.509 |
| No | | 11 (35) | | 14 (25) | | 5 (31) | | | |

Significance level $p<0.05$.
PPS: post-polio syndrome; VAS: visual analogue scale.

patients with PPS who are not suitable for IVIG treatment. Muscle weakness and atrophy in the lower extremities only differed significantly between the positive-responders and non-responders with Vitality as outcome; no differences were seen with Bodily pain as outcome.

The results of this study show that participants had either a positive response in both outcome variables or an improvement in one but not the other. One might speculate that fatigue and pain in PPS are different phenomena, as has been suggested previously by Jensen et al. (31). One may speculate that the reduction in pain and/or fatigue after IVIG treatment defining the positive-responders may indicate an ongoing inflammatory process not seen in the negative-responder group. Increase in muscle fatigue and/or general fatigue were two inclusion criteria, it is possible that these fatigue types have different origins and that only one is improved by treatment with IVIG, for instance if one has a non-inflammatory origin and the other is related to an inflammatory process.

Positive-responders in the 2 outcome variables could be identified by a high level of fatigue and pain, a VAS score above 20, and muscle weakness and atrophy in the lower extremities. The opposite was seen in negative-responders. The results of the present study emphasize the importance of understanding the background of fatigue and pain in PPS. It is possible that the negative-responder group did not reach a critical level of fatigue. If this is the case, the cut-off of fatigue remains to be defined. For pain, this level seems to be a VAS-pain score above 20.

### *Study limitations*

This study has some weaknesses. It has an open trial design, which leads to an increased possibility of a placebo effect. There was no control group, which reduces the generalizability of the results. The variables included in the present study were based on the significant predictors identified by Östlund et al. (23); however, the number of comparisons was relatively large, thus increasing the risk of finding significance of less relevance. In further studies all patients without a suspected progressive course of their symptoms should be excluded in order to eliminate negative-responders.

### *Conclusion*

Bodily pain in particular, but also Vitality, seems to function as outcome after IVIG treatment of patients with PPS. A VAS-pain score above 20 before treatment may be a predictor of a positive outcome for fatigue and pain. Self-evaluation of own health one year previously compared with present health appears to be of value for prediction of positive-responders, as well as negative-responders, indicating a progressive and a non-progressive course, in which the latter may be related

to a negative response. Lack of fatigue and pain as symptoms may be an indicator for exclusion from IVIG treatment. Different patterns of positive response were seen: less fatigue and pain or a reduction in fatigue, but not pain or a reduction in pain but not fatigue. Since IVIG dampens an inflammatory process, it may be that there are fatigue and pain that are either inflammatory or non-inflammatory, influencing the experience of fatigue and pain in the patient, and thus explaining the different combination of positive outcomes. Future studies should investigate fatigue more thoroughly, including its origin and the definition of cut-off scores.

The difference in response shown in this study is seen not only in patients with PPS, but also in those with other diagnoses (21, 22, 32, 33). The identification of negative-responders prior to treatment is important so that this group can be excluded. In this study responders were identified at the group level, the next step will be to identify responders at the individual level.

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