Fatigue, Pain, Anxiety and Depression in Guillain–Barré Syndrome and Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Key Words

Anxiety/depression · Fatigue · Immune-mediated polyneuropathies · Intravenous immunoglobulin · Pain

Abstract

Background: In the clinical evaluation of patients with Guillain–Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), scant attention is paid to symptoms such as fatigue, pain and anxiety/depression. We aimed at addressing seminal studies that focused on the burden of these symptoms and their impact on quality of life (QoL) in these conditions. **Summary:** Fatigue, pain, and anxiety/depression are increasingly being recognized in patients with GBS and CIDP, although their pathophysiological provenance remains unknown. Fatigue and pain are significant in terms of prevalence and intensity, may be a presenting symptom, and can persist for years after apparent functional recovery, suggesting residual injury. Anxiety/depression has also been examined although studies are limited. Despite their negative impact on QoL, the long-term dynamics of these symptoms in patients with GBS and particularly CIDP receiving therapy in routine clinical practice have not been systematically evaluated. Such observations formed the basis for the ongoing (GAMEDIS) studies evaluating the effect of Gamunex[®] on fatigue and depression in patients with CIDP, of which some preliminary data are pre-

sented. **Key Messages:** Strength and sensory deficits are the main areas of focus in patients with GBS and CIDP, but they do not explain the total reduction in QoL, suggesting the possible role of other complaints. A more comprehensive approach to patient care demands that factors such as pain, fatigue and anxiety/depression receive greater attention. The non-interventional GAMEDIS studies are expected to provide valuable insight into the long-term effectiveness of Gamunex[®] in everyday practice.

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Introduction

Strength and sensory deficits dominate the clinical picture and outcome assessments in clinical trials of patients with inflammatory neuropathies, and account for 40–50% of the reduction in quality of life (QoL) expectations [1–3]. Conversely, the remaining 50–60% of the decrement in QoL expectations can be attributed to other factors. In this review, we focus on cardinal studies in patients with Guillain–Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) that examined fatigue, pain, and anxiety/depression. In addition, since the long-term dynamics of fatigue, pain, and anxiety/depression in patients with GBS and particularly CIDP receiving therapy in routine clinical

Fig. 1. Median FSS scores in patients with immune-mediated polyneuropathies compared with HC (a); by disease (b); by gender (c). HM = Healthy male; HF = healthy female; MP = male patient; FP = female patient. Reproduced with permission from [6].

practice have not been systematically examined, we also address preliminary results of the large ongoing (GAMEDIS) studies evaluating the effect of Gamunex® (10% caprylate-chromatography purified immune globulin intravenous (IGIV-C); Grifols) on fatigue and depression in patients with CIDP, under conditions resembling the daily clinical setting.

Fatigue in Immune-Mediated Neuropathies

Chronic fatigue is a common symptom in neurological diseases and can be defined based on its location in the body. Peripheral fatigue is characterized by failure to sustain the force of muscle contraction [4]. Central fatigue, in contrast, is characterized by an enhanced perception of effort and limited endurance of sustained physical and mental activities [4]. Although the underlying mechanism of fatigue has yet to be elucidated, it is believed to be multifactorial, involving both peripheral and central processes [5].

The concept of examining fatigue as an outcome in immune-mediated polyneuropathies derived initially from a patient's request to have fatigue measured in addition to his strength and sensory deficits. The European Inflammatory Neuropathy Cause and Treatment (INCAT) group subsequently designed a study to determine the prevalence and severity of fatigue using the Fatigue Severity Scale (FSS) in patients with immune-mediated polyneuropathies [6]. The FSS is a 9-item self-report questionnaire that measures fatigue severity and the impact of fatigue on a person's activities and lifestyle. Responses are scored on a 7-point scale (1 = strongly disagree to 7 = strongly agree; score range 9–63; a higher score indicating more fatigue).

The INCAT group study involved 113 patients with previous GBS, a clinically stable CIDP or a polyneuropathy associated with monoclonal gammopathy of undetermined significance (MGUSP), and 113 age- and gender-matched healthy controls (HC). In addition to the FSS, other scales used to measure the residual effects of disease included the Medical Research Council (MRC) sumscore, functional grading scale (f-score), INCAT sensory sumscore and the 36-item short-form (SF-36) health survey [6].

The mean FSS score was significantly higher in patients than in HC (6.2 vs. 2.9; $p < 0.0001$; fig. 1) [6]. Severe fatigue (defined as FSS >5) was present in about 80% of patients. The level of fatigue was similar in the GBS and CIDP groups, and marginally lower in the MGUSP group. In general, females reported a higher level of fatigue than males, an observation that was also evident among HC. No significant associations were found between FSS scores and values recorded for general strength, sensory deficits, GBS-disability score or symptom duration. Severe fatigue was reported in 81–86% of patients with normal strength or sensation, and the level of fatigue was similar between ambulatory and wheelchair-bound patients.

In contrast, fatigue was associated with a negative impact on patients' QoL. SF-36 health status scores were significantly lower for patients than for HC, and the correlations between FSS scores and SF-36 scores differed by condition. In the GBS group, the strongest correlations were found in the domains of social functioning (SF; $r = -0.42$, $p = 0.0001$) and vitality ($r = -0.57$, $p < 0.0001$), while moderate, but significant, associations were also observed for mental health (MH; $r = -0.30$, $p = 0.006$) and role-emotional ($r = -0.22$, $p = 0.04$). Correlation with the

socio-emotional domains of the SF-36 is thought to reflect the 'coping' element associated with a monophasic illness such as GBS. In the chronic group (i.e. CIDP/MGUSP), the strongest correlations were found in the physical-oriented dimensions of the SF-36, specifically, general health ($r = -0.65$, $p = 0.0001$) and physical functioning (PhF; $r = -0.53$, $p = 0.002$), possibly reflecting a greater degree of uncertainty surrounding the clinical pattern of these conditions.

Subsequently, the impact of physical training on fatigue in patients with GBS and CIDP was investigated [7]. Twenty patients performed bicycle exercise training 3 times per week for 12 weeks. Although self-reported FSS scores decreased by 21% from baseline to study end (6.1 vs. 4.8, $p = 0.001$), the burden of fatigue remained high. The mean FSS score of 4.8 at week 12 was still near the threshold for severe fatigue and was considerably higher than the mean score of 2.2 reported by HC.

Fatigue can also be a presenting symptom of immune-mediated polyneuropathies as reported in a case series of patients who had been referred for neurological examination due to fatigue [8]. A final diagnosis of CIDP was established in all 11 patients and treatment included intravenous immunoglobulin (IVIG; $n = 8$), corticosteroid ($n = 1$) or cyclophosphamide ($n = 1$). Seven of the 10 treated patients showed significant improvement in fatigue, having a decrease in the mean FSS total score from 49.9 ± 7.0 before treatment to 39.0 ± 9.2 after treatment. The remaining 4 patients, including the untreated patient, had stable disease.

The current clinical literature on fatigue in immune-mediated disorders consists of 11 individual studies/case reports, which involved at least 2 patients with GBS, CIDP, MGUSP or multifocal motor neuropathy [9]. Across all studies, 68% of patients had severe fatigue (FSS >5), emphasizing the fact that fatigue is a serious residual symptom even in patients with apparent good functional recovery.

A review article examined the various fatigue questionnaires available for use (>30), with most being ordinal-based despite the known deficiencies [8, 10–13]. To overcome these shortcomings, the Peripheral Neuropathy outcome measures Standardization (PeriNomS) study group has re-modeled the widely used FSS to a Rasch-built FSS, improving its concept and fulfilling modern clinimetric requirements in GBS and CIDP [14]. All future studies evaluating chronic conditions or conditions with chronic consequences should transform ordinal-obtained data to interval data using, for example, the Rasch method [15].

Pain in Immune-Mediated Neuropathies

The neurological manifestations of immune-mediated disorders are variable and, in some instances, include pain [16, 17]. Although data are limited, a few studies have examined pain and its implications in patients with GBS or CIDP.

Pain in GBS

A prospective study by a Rotterdam group was performed with the specific aim of obtaining more detailed information about pain in GBS and its clinical variants [18]. The study involved 156 patients with newly diagnosed GBS, including 18 patients with Miller Fisher syndrome (MFS). The location, type and intensity of pain were assessed with questionnaires administered at standard time points over a 1-year period.

Pain was experienced across the entire GBS spectrum, including patients with MFS, mild disease or pure motor variants of GBS. Approximately one-third of patients (36%) reported pain as an initial symptom, occurring up to 2 weeks before the onset of weakness. Two-thirds of patients (66%) reported pain during the acute phase of their condition (the first 3 weeks after onset) and 38% of patients reported pain during the first year. The pain type differed between the acute phase (radicular pain, meningism, painful paresthesia/dysesthesia, and myalgia) and chronic phase (painful paresthesia/dysesthesia, myalgia, and joint pain) of GBS although there were some areas of overlap. Among patients with pain, most ($\geq 70\%$) reported moderate to severe pain at each time point during follow-up (table 1). The observation that slightly more than one-third of patients reported severe pain (8–10 points on the 11-point (0–10) Numerical Rating Scale (NRS)) at 52 weeks after onset highlights the significant injury retained by a relevant proportion of patients with GBS.

Pain has also showed some association with intraepidermal nerve fiber density (IENFD) [19]. In the acute phase of GBS (first 3 weeks after onset), IENFD was reduced in 60 and 61.9% of patients at the distal leg and lumbar region, respectively, of which 43.7% of patients reported neuropathic pain. The IENFD at the distal leg was significantly lower in patients with pain than without pain ($p < 0.001$) and correlated significantly, although moderately, with pain intensity ($r_s = -0.51$; $p = 0.003$), even in patients with the pure motor variant of GBS. No association was found between IENFD, clinical dysautonomia and GBS severity at nadir, as had been reported previously [20].

Table 1. Pain severity over time in a prospective study in patients (n = 156) with GBS. Reproduced with permission from [18]

Pain severity, n/n with pain, %	Maximum 2 weeks before onset of weakness	Acute phase	13 weeks	26 weeks	39 weeks	52 weeks
NRS 1–4	6/54 (15)	9/100 (9)	19/84 (23)	17/74 (23)	17/58 (29)	16/55 (29)
NRS 5–7	25/54 (46)	36/100 (36)	30/84 (36)	28/74 (38)	22/58 (38)	20/55 (36)
NRS 8–10	21/54 (39)	50/100 (50)	28/84 (33)	26/74 (35)	18/58 (31)	19/55 (35)
Unknown	0	5/100 (5)	7/84 (8)	3/74 (4)	1/58 (2)	0

Pain in CIDP

Although pain is typically regarded as a secondary sign of CIDP, Boukhris et al. [21] described the characteristics of 5 patients in whom pain was the main cause of referral and the most prominent symptom. Patients presented initially with pain in the lower limbs associated with modest motor impairment (1 case), distal paresthesia (4 cases), cramps (1 case) and fatigue (2 cases). After extensive work-up including nerve biopsy, a diagnosis of CIDP was established in each case. All patients received symptomatic treatment and 4 patients received immunomodulatory treatment, which was consistently effective. Scores on the 0–10 visual analogue scale for pain were significantly lower after vs. before treatment (4.1 vs. 9.0; $p = 0.01$).

In the cross-sectional survey study from the Netherlands, median pain severity as measured on the 0–10 NRS was mild and scores for patients with GBS or CIDP were similar: 2.2 vs. 2.3 points [22]. However, the proportion of patients with CIDP reporting severe pain (NRS ≥ 7) was twofold higher than in patients with GBS (17 vs. 8%; $p = 0.028$).

In the United Kingdom, Goebel et al. [23] investigated the intensity and distribution of pain in 24 patients with CIDP. Pain intensity was categorized as mild (NRS 0–3) in 62% of patients, moderate (NRS 4–6) in 26% of patients, and severe (NRS 7–10) in 13% of patients. In this patient sample, pain typically had a distal distribution, suggestive of a length-dependent, primarily neuropathic mechanism. On the basis of their findings, the investigators concluded that ‘the notion of CIDP as a painless disorder should be revisited’.

Anxiety/Depression in Immune-Mediated Neuropathies

Although chronic conditions are known to impact adversely on a person’s mental state and psychiatric health [24], only a few studies have examined the psychological

health status in patients with immune-mediated neuropathies.

The survey study conducted in members of the Dutch Society of Neuromuscular Disorders found that approximately 1 in 15 (6.7%) of patients with GBS and 1 in 11 (9%) patients with GBS or CIDP had depression based on Hospital Anxiety and Depression Scale scores [22].

Another group investigated psychological distress, depressive symptoms, and the health status of patients during the first year after a diagnosis of GBS [25]. At 3, 6 and 12 months post-diagnosis, patients (n = 85) were administered the General Health Questionnaire, Sickness Impact Profile, and Center for Epidemiologic Studies Depression Scale. Psychological distress and depressive symptoms were present at 3 months but improved notably between 3 and 6 months. While some degree of impairment of patients’ psychosocial health status was still evident at 12 months, depressive symptoms had abated.

In a bicycle exercise training study in patients with GBS and CIDP, it was shown that physical training led to significant relief of anxiety and depression (table 2) [7]. Nevertheless, the impact of physical training on patients’ health status was more apparent in the physical component summary (PCS) vs. the mental component summary (MCS) of the SF-36.

QoL in Immune-Mediated Neuropathies

QoL has been defined as ‘the patient’s reaction to the discrepancy between actual and expected achievements arising as a consequence of being ill’ [26]. In general terms, QoL assessment encompasses 4 core dimensions (box 1) [27].

A study was undertaken in patients with immune-mediated polyneuropathies to determine whether QoL assessments complement conventional outcome measures [1]. The SF-36 health survey and 3 other measures (MRC sumscore, sensory sumscore, and Hughes functional

Table 2. Anxiety/depression and SF-36 health status scores in patients with chronic inflammatory demyelinating polyradiculoneuropathy during bicycle exercise training. Adapted from [7]

Variable	Exercise group (n = 20)			Healthy individuals (n = 10)
	baseline (n = 20)	6 weeks (n = 17)	12 weeks (n = 18)	baseline (n = 10)
HADS				
Anxiety	1.89±0.48	1.71±0.36	1.59±0.30 [†]	1.44±0.32 [‡]
Depression	1.71±0.37	1.55±0.44	1.39±0.28*	1.26±0.32 [‡]
SF-36				
PCS	44.0	45.6	50.1 [†]	58.4 [‡]
MCS	51.6	52.7	55.9	55.7

* p < 0.01 vs. baseline; [†] p < 0.05 vs. baseline; [‡] p < 0.01 vs. baseline values of exercise group; HADS = Hospital Anxiety and Depression Scale.

Box 1. Quality-of-life dimensions [27]

Physical health	Mainly disease-related and treatment-related symptoms
Functional health	Self-care, mobility, and physical activity level; capacity to carry out various roles in relation to family and work
Psychosocial life	Cognitive functioning, emotional status and general perceptions of health, well-being, life satisfaction and happiness
Social functioning	Qualitative and quantitative aspects of social contacts and interactions

scale) were assessed in 114 patients with clinically stable disease (GBS: 83, CIDP: 23, MGUSP: 8), and serially in 20 patients with recently diagnosed GBS (n = 7) or CIDP (n = 13) and changing conditions who were examined longitudinally (period: 1 year). All latter patients, except one, were treated with IVIG. Values recorded on the SF-36 for both populations were compared with scores reported for the healthy Dutch community (controls).

In the cross-sectional group with stable disease, SF-36 scores were substantially lower compared with healthy Dutch control data (p < 0.0001). The impact of disease on patients' health status was greater for the physical domains compared with the socio-emotional domains of the SF-36 (fig. 2). In the longitudinal group, treatment-related improvement resulted in a gradual shift of all SF-36 scores toward normal values, although they were still somewhat lower than published normative data.

To date, the ICE study (IVIG for treatment of CIDP) is the largest trial to have been performed in patients with CIDP [28]. In this randomized, double-blind, response-conditional, crossover trial, 117 patients received IGIV-C or placebo every 3 weeks for up to 24 weeks in the first treatment period. Participants whose

INCAT disability score had not improved by ≥1 point were switched over to the alternate treatment in a 24-week crossover period [28]. In either treatment period, participants who improved and completed treatment were eligible to be randomly reassigned to IGIV-C or placebo in a 24-week extension phase. QoL assessments were conducted using the SF-36 health survey, and results were reported separately from the efficacy and safety findings [29].

In the first 24-week period, improvements in all SF-36 domains favored IGIV-C over placebo, with values for PhF, role-physical, SF, and MH reaching statistical significance (p < 0.05); a trend was apparent in favor of IGIV-C over placebo in the domains of bodily pain, general health, vitality and role-emotional (fig. 3). Overall, treatment-related improvement with IVIG-C showed significance in the PCS score (5.7 vs. 1.3; p = 0.020) but not the MCS score (3.3 vs. 0.9; p = 0.241; fig. 3). Similar general trends were observed in the crossover period. During the extension phase, mean improvements in SF-36 scores that had been achieved during the initial 24-week treatment phase were generally increased or maintained in patients re-assigned to IGIV-C, whereas pa-

Fig. 2. SF-36 health status scores in (I) the general Dutch population and (II) the group of patients (n = 114) with clinically stable immune-mediated polyneuropathies (GBS, chronic inflammatory demyelinating polyneuropathy, gammopathy-related polyne-

ropathy). RFPh = Role functioning–physical; RFE = role functioning–emotional; BP = body pain; Vit = vitality; GHP = general health perception. Reproduced with permission from [1].

Fig. 3. QoL in patients with CIDP during 24 weeks' treatment with 10% IGIV-C (Gamunex®) in the ICE study. Reproduced with permission from [29]. * p < 0.05. LSM = Least squares mean.

tients re-randomized to placebo experienced worsening. SF-36 scores at baseline and after 24 and 48 weeks of treatment gradually regressed to normal values in patients who had been treated with IVIG-C for 48 weeks.

Non-Interventional Study of Gamunex® in CIDP

Clinical studies evaluating the efficacy of IVIG in patients with CIDP generally focus on muscle weakness, sensory deficit and functionality. No study to date in

CIDP has longitudinally examined the influence of IVIG on fatigue and depression dynamics in this condition. In the non-interventional GAMEDIS (GAMunex Müdigkeit Depression Sicherheit; Gamunex fatigue depression safety) study from Germany, changes in depression and fatigue dynamics over time were assessed in patients with CIDP treated for up to 48 weeks with IVIG. To ensure that the patient population reflected everyday practice, inclusion and exclusion criteria were kept to a minimum. Basically, all patients with a CIDP diagnosis by their treating physician, who provided signed in-

formed consent, were eligible to participate. The sole exclusion criterion was a selective IgA deficiency. Primary outcome measures were change in depression levels on the Beck Depression Index (BDI), and change in fatigue on the FSS, from study entry through to week 48, examined initially in the traditional ordinal manner. At a later stage, most ordinal-based measures will be transformed to meet modern scientific requirements. Secondary outcomes were therapeutic benefit as assessed by IVIG therapy, general health, INCAT disability score and Hughes functional score from study entry through to week 48. Safety was assessed by documenting all adverse events that occurred during the study.

Patients completed the BDI and FSS at study entry (visit 1) and every 12 weeks thereafter up to week 48. At each 3-weekly visit, physicians assessed IVIG therapy and general health.

Thus far, 95 patients have been recruited in the GAMEDIS study. Early results indicate that fatigue remains a high burden in CIDP, whereas only a small proportion of the population were at risk for depression. IVIG has shown good safety and tolerability during long-term treatment.

Patients who completed the GAMEDIS study became eligible for enrollment in the GAMEDIS 2 study, which is extending the total observation period to 3 years. In addition to the BDI and FSS, outcome measures for patients in GAMEDIS 2 include the SF-36 health survey and Work Productivity and Activity Impairment questionnaire.

Study recruitment took place between October 2012 and December 2013 and the observation period extends from October 2012 to December 2015.

Conclusions

Fatigue, pain and anxiety/depression contribute to QoL impairment in patients with immune-mediated polyneuropathies. Since these symptoms are less tangible than strength and sensory deficit, the underlying mechanisms are not fully understood. Greater research efforts to unravel their pathophysiological mechanisms (e.g. sodium channel pathogenicity for pain?) might be expected to contribute to prognosis in immune-mediated polyneuropathies.

Although the evidence base is limited, studies that have investigated fatigue, pain and anxiety/depression in patients with GBS and CIDP have provided useful insights. Fatigue and pain can persist for many years after diagnosis, adding to the burden of disease. As fatigue and

pain can also be presenting symptoms of GBS or CIDP, vigilance is required during differential diagnosis. Treatment with IVIG-C can produce relevant improvements in patients' QoL, especially for the physical components of health status.

The efficacy of IVIG-C in CIDP patients was demonstrated in the ICE study. The ongoing GAMEDIS study from Germany is the first multicenter, non-interventional trial to investigate the treatment effects of IVIG (Gamunex® 10%) in CIDP patients in routine clinical practice, including assessment of depression and fatigue. Early results are in general agreement with observations from clinical studies. Final results will be reported in the near future.

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