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The life situations of patients with primary antibody deficiency untreated or treated with subcutaneous gammaglobulin infusions

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SUMMARY

The life situations of 25 patients with hypogammaglobulinaemia were studied before and after the initiation of subcutaneous replacement therapy by using medical records, data registers and questionnaires (a study and a disease-specific questionnaire, the Sickness Impact Profile and the General Health Rating Index). Before treatment, the patients perceived more dysfunctions with regard to ambulation, mobility, emotional behaviour, social interaction, sleep and rest, household management, work and recreation or pastime activities compared with a Swedish reference group ($P=0{\cdot}0001$). A significant increase in the perceived frequency of infections was also seen in untreated patients compared with a group of healthy individuals ($P=0{\cdot}0001$). After 18 months of weekly subcutaneous infusions of an intramuscular gammaglobulin preparation (100 mg/kg), the patients reported a significantly increased, health-related function and improved self-rated health. A significantly higher pre-infusion IgG level was also found.

Keywords hypogammaglobulinaemia gammaglobulin treatment quality of life health

INTRODUCTION

Primary antibody deficiencies, such as common variable immunodeficiency (CVID), X-linked agammaglobulinaemia (XLA) or thymoma with hypogammaglobulinaemia, lead to an increased rate of recurrent respiratory tract and gastrointestinal infections [1]. Patients prone to infections benefit from substitution therapy with gammaglobulin, which reduces both the rate and the severity of the infections [2]. For many years, this lifelong replacement therapy was given in the form of intramuscular injections or plasma infusions. During the 1980s, suitable intravenous preparations were developed, and this form of administration was frequently used [3–9], but was subsequently replaced in our clinic by subcutaneous infusions of an intramuscular gammaglobulin preparation [10].

There has been a growing awareness of the importance of a better understanding of patients' life situations in terms of self-rated health and perceived functional status, as it has been found that a poor self-rated health status, apart from sex and age, is a predictor of mortality, independent of physical status [11–13]. To our knowledge, the life situations of patients with primary antibody deficiencies have not been systematically studied before. The aims of the study were (i) to describe the life situations of untreated patients with hypogammaglobulinaemia and to compare this group of immunodeficient patients with healthy controls and groups of patients with other chronic or acute diseases, and (ii) to investigate whether weekly subcutaneous gammaglobulin infusions had any impact on the life situations of patients with hypogammaglobulinaemia.

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PATIENTS AND METHODS

Patients

From two hospitals in the Stockholm area and from one hospital in the southern part of Sweden, all patients aged 18 years or older with a diagnosis of hypogammaglobulinaemia were invited to participate in the study. Twenty-five patients remained when individuals unable to read and write Swedish, mentally unable to answer questionnaires, chronically ill with other diseases or abusing alcohol or drugs had been excluded ($n=3$). All 25 patients—constituting the treated (T) group—were given subcutaneous treatment as self-infusions once a week (100 mg/kg per week) [10]. After an introductory period at the hospital (2–6 months), the infusions were taken at home. The patients answered four questionnaires both before and after 18 months of subcutaneous gammaglobulin therapy. At the time of initiating the subcutaneous treatment, the total T group ($n=25$) consisted of 15 patients receiving on-going intramuscular or intravenous gammaglobulin therapy and 10 patients previously untreated with gammaglobulin. The latter constituted an

untreated (UT) group and data from the questionnaires answered by these patients before starting the subcutaneous treatment will be presented separately.

The mean age for the 12 men and 13 women in the T group was 43 (s.d. 16, range 18–66) years. Twenty-three patients had a CVID, one a XLA and one a thymoma with hypogammaglobulinaemia. The mean serum IgG level at the time of diagnosis was 1·6 (s.d. 1·3, range 0·1–4·2) g/*l*, IgA 0·06 (s.d. 0·1, range 0·01–0.32) g/*l* and IgM 0·2 (s.d. 0·3, range 0·03–1.6) g/*l*, respectively. The duration from onset of the symptoms to the diagnosis differed between 1 and 56 (median 10) years. Of the 15 patients receiving on-going gammaglobulin treatment at the time of initiating the subcutaneous therapy, 13 had had substitution therapy with intramuscular injections and two with intravenous infusions for a mean period of 78 months. Seventeen patients were working full or part time, three were retired, three were students, and two were on sick-leave for more than 6 months.

The UT group consisted of nine of the patients with a CVID and the patient with a thymoma with hypogammaglobulinaemia. The mean age for the 10 patients (five men, five women) was 38 (s.d. 14, range 18–58) years.

Reference groups

Eight reference groups (A–H) were used. A was a randomly sampled group of adults ($n=145$) from Stockholm County. From this group, individuals from the corresponding age range as the immunodeficient patients were selected, forming a subgroup of 95 individuals, 45 men and 50 women, with a mean age of 40 years [14]. B consisted of kidney transplant patients with functioning grafts ($n=144$, 81 men and 63 women, mean age 37·2 years) [15]. C was a group of patients with rheumatic disorders, such as rheumatoid arthritis, polyarthritis and osteoarthritis ($n=147$, women, age range from 38 to 72 years) [16]. D were patients using haemodialysis at home ($n=286$, 184 men and 103 women, mean age 47 years) [15]. E were patients using hospital-based dialysis ($n=53$, 24 men and 29 women, mean age 60 years) [17]. F were patients on peritoneal dialysis ($n=81$, 37 men and 44 women, mean age 49·8 years) [15]. G were patients with acute low back pain ($n=90$, 30 men and 60 women, mean age 43·3 years) [18]. H were participants in a nursing conference ($n=133$, eight men and 125 women, mean age 43·2 years).

The Swedish reference group (A) did not differ as regards age and sex distribution, compared with the UT or the T group. The reference groups B–H were used only in comparison with the untreated, immunodeficient patients; significant differences were found regarding the sex distribution between the UT group and reference groups C and H. The UT group was significantly younger ($P<0·05$) compared with reference group E.

Methods

Four questionnaires were used to collect self-reported data.

1 Demographic and social data were collected by using 12 items from a study-specific, 126-item questionnaire.
2 A 67-item, disease-specific questionnaire was developed for the study. The items used for this study concerned the patients' own perceptions of infections and ability to participate in social and recreational activities. The items had the answer format of a visual analogue scale (VAS) ranging from 1 to 100 mm, yes or no, or open-ended answers.
3 The Sickness Impact Profile (SIP) is a behaviourally based measure of health-related dysfunctions (136 items) [19]. It was developed in order to provide a measure of self-rated health status in both chronically and acutely diseased subjects. The SIP items are grouped into 12 subscales: ambulation, body care and movement, mobility, emotional behaviour, social interaction, alertness behaviour, communication, sleep and rest, household management, work, food intake and recreation or pastimes. A percentage score is obtained for the total SIP as well as for the 12 subscales. The higher the scores, the poorer the patients' perceived, health-related, functional status. The SIP has previously been translated into Swedish and evaluated in Sweden [14,20].
4 The General Health Rating Index (GHRI) consists of 29 items designed to measure multiple dimensions of an individual's self-rated general health. The items have the format of a five-point Likert scale, ranging from definitely true to definitely false. Six subscales can be distinguished: perceptions of past, present and future health, health-related worries and concerns, susceptibility to illness and tendency to view illness as a part of life [21]. The higher the scores, the better the self-rated health. The GHRI has been translated into Swedish and evaluated in Sweden (data unpublished, Sullivan).

A physical status and blood samples for laboratory investigations were obtained from each patient the same day as the questionnaires were filled in. Pre-infusion samples for serum IgG, IgA, IgM and IgG subclasses were collected.

Data about disease duration were obtained from the patients' medical records and by interviewing the patients. Data about the number of days in hospital and the number of visits to a doctor on account of infections were obtained from the patients' medical records and from the Stockholm County Council's data registers. Permission to use the data registers was given.

The study protocol was approved by the Ethical Committees at the Huddinge University Hospital and the Karolinska Institute. Informed consent was obtained from all patients.

Statistical analysis

Since not all the variables were normally distributed, non-parametric methods were used. Statistical significance was accepted if $P<0·05$. The differences between groups were tested by the Wilcoxon–Mann–Whitney test and differences over time by Friedman's test. Relations between variables were expressed in Spearman rank-order correlation coefficients. Nominal data were treated by Fisher's exact test. However, since individual scores from the SIP test were not always available in the published studies, the statistical comparison between the UT group and reference groups A–G was made by Student's *t*-test.

RESULTS

Patients previously untreated with gammaglobulin (UT group) before subcutaneous therapy

The Sickness Impact Profile. The means for the total SIP scores for the 10 previously untreated patients (mean 5·3, s.d. 2·9), as well as for reference groups A–G, are shown in Fig. 1. A significant difference was found between the UT group and the Swedish reference group ($P=0·0001$); thus, the immunodeficient patients rated their health-related, overall functional status as poorer. Significantly higher scores were found for the

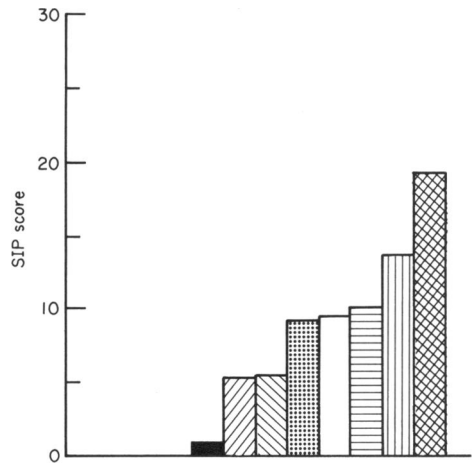

Fig. 1. Mean, total Sickness Impact Profile (SIP) scores for a Swedish, randomly sampled reference group ($n=95$), patients with hypogammaglobulinaemia untreated with gammaglobulin (UT group, $n=10$), patients with functioning kidney grafts ($n=144$), with rheumatic disorders ($n=147$), on haemodialysis at home ($n=286$), on hospital-based haemodialysis ($n=53$), on peritoneal dialysis ($n=81$) and with acute low back pain ($n=90$). The higher the score, the poorer the subjects' perceived, total, health-related, functional status. ■, Swedish reference group; ▨, UT group; ▧, kidney transplants; ▦, rheumatic disorders; □, home haemodialysis; ▤, hospital haemodialysis; ▥, peritoneal dialysis; ▩, acute back pain.

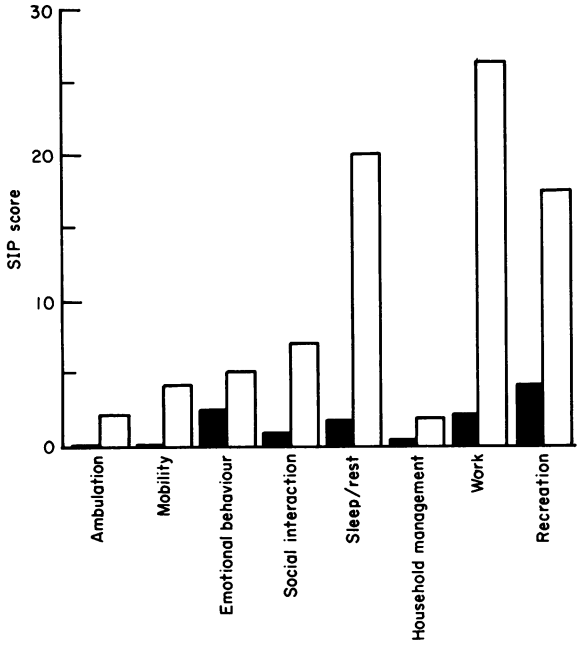

Fig. 2. The mean Sickness Impact Profile (SIP) scores for the eight subscales in which significantly poorer functional status was found for untreated patients with hypogammaglobulinaemia (UT group, $n=10$), compared with a Swedish, randomly sampled reference group ($n=95$): ambulation ($P<0.01$), mobility ($P=0.0001$), emotional behaviour ($P<0.05$), social interaction ($P=0.0001$), sleep and rest ($P=0.0001$), household management ($P<0.01$), work ($P=0.0001$) and recreation or pastime ($P=0.0001$). ■, Swedish reference group; □, UT group.

patients on hospital-based haemodialysis ($P<0.05$) and peritoneal dialysis ($P<0.01$) and, as expected, for patients with an acute pain disorder ($P<0.01$), as compared with the UT group. No significant differences were seen between the UT group and the kidney transplant patients, the patients with rheumatic disorders and the patients on haemodialysis at home. Significantly higher scores were seen in the UT group for eight of the SIP scales, compared with the Swedish reference group (Fig. 2).

Infections. Nine patients perceived themselves as often being infected (scores >50 on the VAS with 100 always infected). The mean score was 79 (s.d. 25, median 88·5, range 20–100). In order to study whether there was a difference in the perception of the frequency of infections among individuals with hypogammaglobulinaemia and others, the same question was asked of a group of 133 persons (reference group H). The mean score obtained for reference group H was 16 (s.d. 17, median 12, range 1–97) ($P=0.0001$). Questions addressed to the UT group about their general fear of getting infected and of getting infections in special situations, as when visiting or staying in groups of people (100 always afraid), had the mean scores of 67 (s.d. 27, median 72·5, range 24–99) and 63 (s.d. 31, median 71, range 5–99), respectively. Half of the patients said that they actively tried to avoid infections by not using public transport services and by avoiding persons with respiratory tract infections.

Patients treated with subcutaneous infusions of gammaglobulin (T group)

Since the T group ($n=25$) at the time of initiating the subcutaneous gammaglobulin treatment consisted of patients both receiving ($n=15$) and not receiving ($n=10$) on-going gammaglobulin treatment, every variable was tested, in order to investigate whether differences existed between these two groups. When nothing else is stated, no differences were found.

The Sickness Impact Profile. Before starting the subcutaneous treatment, significantly poorer functional status was rated by the total T group ($n=25$), compared with the Swedish reference group ($P<0.05$), for the total SIP score and the subscales mobility, sleep and rest, household management, work and recreation or pastimes. After 18 months of subcutaneous therapy, significant differences between the T group and the reference sample were only found for the scales ambulation ($P<0.05$), mobility ($P<0.01$) and social interaction ($P<0.05$).

Significantly poorer functional status was rated within the T group by the 10 previously untreated patients, compared with the 15 previously intramuscularly or intravenously treated patients, before starting the subcutaneous therapy for the following scales: total SIP ($P<0.05$), sleep and rest ($P<0.05$) and work ($P<0.01$). No such differences were found after 18 months of subcutaneous treatment.

The General Health Rating Index. The patients in the total T group rated their total ($P<0.05$) and current health ($P<0.01$) as better after 18 months. The mean, total index score before the subcutaneous treatment was 62 (s.d. 14) and at the follow up after 18 months 72 (s.d. 15) (maximum score=110). The corresponding scores for the subscale current health were 27 (s.d. 9) and 33 (s.d. 7), respectively (maximum score=45). The total GHRI scores correlated negatively with the total SIP scores both before and after 18 months of treatment ($P<0.01$ and $P<0.05$, respectively). Thus, the better the perceived general health, the better the perceived functional status.

Table 1. Perception of infections in 25 patients with primary hypogammaglobulinaemia before and after 18 months of subcutaneous gammaglobulin treatment

	Before treatment			After 18 months of treatment			
	Mean	(s.d.)	Median	Mean	(s.d.)	Median	
Perceived							
Frequency of infections	75	(23)	84	44	(28)	46	$P<0.001$
General fear of getting infections	57	(24)	55	36	(30)	27	$P<0.01$
Anxiety for own future health	57	(25)	60	35	(25)	34	$P<0.01$

Score 100, Always infected/always afraid.

Infections. On account of infections during the 12 months preceding the subcutaneous treatment, the patients in the total T group had visited a doctor 1–27 (mean 7) times. Five patients were admitted to hospital for 8–37 (mean 17) days, on account of respiratory tract infections during the 18 months preceding the subcutaneous treatment. The corresponding data after the introductory 18 months of subcutaneous treatment were 1–6 (mean 3) visits to a doctor and 5 days in hospital for one patient.

The patients perceived a decreased frequency and fear of infections, as well as a decreased anxiety for their own future health (Table 1) after 18 months on subcutaneous therapy. Negative correlations were found between the frequency of infections and the total GHRI scores (i.e. the lower the frequency of infections, the better the rated health) both before and after 18 months of treatment ($P<0.001$ and $P<0.01$, respectively).

Recreational and social activities. Before starting the subcutaneous therapy, the patients in the T group receiving on-going, intramuscular or intravenous gammaglobulin therapy ($n=15$) reported that they found it more difficult to decide how to spend their holidays, compared with the 10 previously untreated patients ($P<0.05$). However, after 18 months of subcutaneous treatment this difference could not be found.

After 18 months of subcutaneous treatment, the patients also reported an increased ability to participate in recreational activities ($P<0.01$). No significant score changes were seen during the treatment concerning the patients' perceptions of planning and participation in different social activities.

Immunoglobulin levels. At the time of starting the subcutaneous therapy, the mean, pre-infusion IgG level for the patients in the T group receiving on-going, intramuscular or intravenous gammaglobulin treatment ($n=15$) was 4·4 (s.d. 3·0, range 0·7–12·5) g/*l*. After 18 months of subcutaneous treatment, it had increased to 9·8 (s.d. 1·5, range 7·5–12·5) g/*l* ($P=0.0001$). For the previously untreated patients in the T group ($n=10$), the mean, pre-infusion IgG level was 1·9 (s.d. 1·5, range 0·2–4·2) g/*l* before and 9·1 (s.d. 1·3, range 7·0–10·9) g/*l* after 18 months ($P<0.001$) of treatment. A significant difference ($P<0.05$) was found with regard to IgG levels between the previously intramuscularly or intravenously treated and previously untreated individuals in the T group before, but not after 18 months of subcutaneous infusions.

DISCUSSION

The previously untreated patients in this study reported a poorer functional status, compared with a Swedish reference group. The detailed, functional profile obtained by using the SIP test indicates that patients with hypogammaglobulinaemia not yet treated with gammaglobulin perceive restrictions in several areas of their daily life: in ambulation, i.e. they have to walk more slowly, walk shorter distances or stop to rest often; in decreased physical mobility, i.e. they have to stay in bed more or are unable to use public transport; in emotional behaviour, in social and leisure activities, in home management and in doing their work. They were also tired and in need of more sleep and rest. The overall, functional status for these patients was compared with the functional status of patients with other chronic or acute diseases. The investigation showed that the functional status of the immunodeficient patients is comparable with the functional status of patients with other chronic diseases such as renal failure and rheumatic disorders. With this comparison, we hope to make health care personnel more aware of the impact that hypogammaglobulinaemia may have on the patients' daily life, since this group of patients does not usually have any visible impairments or handicaps.

Patients with untreated hypogammaglobulinaemia were found not only to perceive a high frequency of infections, but also to have a fear of getting these infections. To be able to live with the disease, many in this group of individuals had developed certain coping strategies to try to minimize the risks of getting infections, for example avoiding the use of public transport systems, groups of people and persons with known, on-going, respiratory tract infections. However, this sometimes results in further restrictions on daily life.

This study also showed that the use of weekly, self-administered, subcutaneous infusions of gammaglobulin led to a better functional status, improved general health and to higher pre-infusion IgG levels for both the previously untreated and the previously intramuscularly or intravenously treated patients. This is further confirmed by the decreased numbers of patients admitted to the hospital and by the fewer visits to the doctor on account of respiratory tract infections. To what extent other factors, such as effective treatment with antibiotics, influenced the outcome cannot be answered in this study. However, the 15 patients who previously received intramuscular or intravenous treatment had been cared for at the same hospitals. This means that most of the patients included in the T group had received the same medical and nursing care as during the later subcutaneous treatment.

Before starting the subcutaneous therapy, the patients in the T group receiving on-going, intramuscular or intravenous gammaglobulin therapy reported that they found it more difficult to decide how to spend their holidays, compared with

the untreated patients. One interpretation may be that the patients, when receiving intramuscular or intravenous therapy, experienced a limitation in their choices of when and where to spend the holidays since they needed help with their treatment. The patients' independence has now increased, as they are using self-infusions at home.

The subcutaneous form of administration has recently been shown to be safe and is appreciated by the patients [10,22]. Our results in this study indicate that the method of giving the substitution therapy as subcutaneous infusions leads to improvements in the patients' quality of life. However, these results should be taken with caution, as the sample is small and there are—as far as we know—no other such results with which to compare them. Furthermore, it was not the aim of this study to compare subcutaneous treatment with other administration regimens. Despite these limitations, we believe that many of the patients on life-long, substitution treatment with gammaglobulin would benefit from subcutaneous therapy.

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