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Health-Related Quality of Life in Primary Antibody Deficiency

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ABSTRACT

Patients with primary antibody deficiencies (PAD) are susceptible to recurrent and chronic infections and a variety of complications. This study was performed to assess quality of life (QoL) of PAD patients who were under long term treatment and regular follow-up.

Thirty six adults with proved diagnosis of PAD, who had received regular intravenous immunoglobulin replacement therapy, were enrolled in this study. The QoL of selected PAD patients was measured by Medical Outcomes Study 36-item Short-Form (SF-36) Health Survey questionnaire.

The patients with PAD showed significantly reduced scores in physical component in comparison with healthy age-sex matched control subjects (60.2±20.1 *vs.* 85.5±4.7, $P<0.001$). Mental component score was also significantly decreased in the patient's group (59.8±19.5 *vs.* 72.3±3.4, $P=0.002$). There was a reverse association between SF-36 scores and number of infections episodes ($r=-0.73$ $P=0.003$). The patients with long delay diagnosis showed significantly lower SF-36 scores ($r=-0.62$, $P=0.003$).

The patients with PAD who were diagnosed timely and managed appropriately seem to have lower complications and better QoL. However, the patients with severe phenotypes and long delay in diagnosis showed lower QoL, even in medical management.

Key words: Common Variable Immunodeficiency; Primary Antibody Deficiency; Quality of Life

INTRODUCTION

Primary antibody deficiencies (PAD) are the most common form of primary immunodeficiency diseases, which include selective IgA deficiency (SIgAD), common variable immunodeficiency (CVID), X-linked agammaglobulinemia (XLA), hyper IgM syndromes (HIGM), IgG subclass deficiencies and specific antibody deficiencies.[1-4] The impaired host defense in these patients leads to an increased susceptibility to recurrent infections.[5] Regular replacement therapy with intravenous immunoglobulin (IVIG) at the doses of 400 to 600 mg/kg is the main treatment to decrease the

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recurrence and the severity of infections.[6] However, IVIG infusion could be associated with a range of side effects such as nausea, headache, chills, fever, rash, hypotension, and hypertension.[7,8] Quality of life (QoL) of patients with PAD could be affected as a consequence of chronicity of disease and side effects of long-term treatments.

Although pre and post treatments measuring of QoL may be applicable for newly diagnosed patients and newly modality for treatment, this method is not useful for chronic patients who are in the regular treatment program and did not have any baseline QoL. In this study, we investigated the QoL in a group of PAD patients who were under regular follow-up and treatment as an impact of PAD diseases.

PATIENTS AND METHODS

Subjects

Thirty six patients with diagnosis of PAD, based on diagnostic criteria defined by European Society for Immunodeficiencies (ESID) and Pan-American Group of Immunodeficiency (PAGID), [9] who were diagnosed at the Children's Medical Center Hospital (Pediatrics Center of Excellence in Tehran, Iran) were selected. The inclusion criteria for patients' enrollment were:

1: patients under regular IVIG replacement therapy with 400-600 mg/kg for every 3-4 weeks;

2: age range between 15 and 45 years;

3: No hospital admission during the last one month;

4: No major stress in previous 3 months;

5: No history of any psychological problem.

Control group of persons was selected hospital based from age and sex matched subjects who were referred to outpatient clinic of Children's Medical Center Hospital. They did not any history of recurrent or chronic infections and showed normal immune responses.

The study was approved by the Ethics Committee of Tehran University of Medical Sciences and informed consents were obtained from all patients. Demographic data, type of PAD, time of diagnosis, duration of treatment were evaluated.

The Questionnaire of QoL

Satisfaction or happiness of person's within areas of life that are affected by health or health care determine the health-related QoL.[10]

The QoL for selected PAD patients was measured by MOS SF-36 (Medical Outcomes Study 36-item Short-Form Health Survey, http://www.qualitymetric.com), which is used for disease-specific studies. This questionnaire can measure various health dimensions specially physical and mental components by eight health related items which include: physical functioning (PF-10 concepts), role limitations due to physical problems (RP-4 concepts), bodily pain (BP-2 concepts), general health perceptions (GH-5 concepts), vitality (VT-4 concepts), social functioning (SF-2 concepts), role limitations because of emotional problems (RE-3 concepts), and mental health (MH-5 concepts).

Moreover another extra item which also has been added in the SF-36 was health transition (change in general health status over a one-year period).[11] There are linguistically validated of translated SF-36 questionnaire by a previously developed survey (forward–back-ward translation processes) and tested in a study involving a random sample of 4163 healthy individuals aged 15 years and over in Tehran.[12]

Statistical Analysis

Standardized subscale ranging from 0 to 100 was measured for summing the total scores from all of the eight domains in which higher scores representing better health status.[11]

The results of QoL in the patients with PAD were compared with selected age matched controls.[12] Correlation analyses were done using Pearson's product moment correlation coefficients. Statistical tests were two-tailed.

Therefore, impact of PAD disease was evaluated by comparison of scales between cases and controls. Two-tailed paired t-tests were used to compare SF-36 scale scores between these two groups. The non-responder rate to single items was very low (in total, 0.43%). However, to handle many observations as possible, missing data for repeated measurements were imputed using an explicit regression model (i.e., repeated measure model with unstructured covariance matrix) that included previously observed scores of the patient as well as the important covariates.[13] Mean value substitution was performed for missing data, if responses for a single scale were less than 50%.[14] Also, an explicit regression model[15] were used for prediction based on scales of the responders.

RESULTS

Patients' Characteristics

Thirty six PAD patients (27 male and 9 female), aged 15-45 years, were included in this study.

All the participants were native Persian speakers and could easily understand the questionnaire. Before the time of study, patients were followed for a total of 316 patient-years with a mean follow-up of 8 ±2.4 years per patient. Table 1 shows the general characteristics, serum immunoglobulin concentrations, and distributions of lymphocyte subtypes in the patients.

Results of SF-36 Questionnaire

Comparison of transformed scores of 36 patients with controls showed that the patients with PAD expressed significantly reduced scores in physical (60.2±20.1 *vs.* 85.5±4.7, $p<0.001$) and mental components (59.8±19.5 *vs.* 72.3±3.4, $p=0.002$). Details of the results of SF-36 scores are presented in the table 2, which indicates that except mental health, other dimensions had showed reduced scores in the patients' group.

By increasing complications in PAD patients, both physical and mental SF-36 scores were decreased. Higher episodes of infections (physical $r=-0.57$, $p=0.002$; mental $r=-0.64$, $p<0.001$), number of different involved organs (physical $r= -0.46$, $p= 0.016$; mental $r=-0.51$, $p=0.008$) and number of hospitalization (physical $r=-0.04$, $p=0.09$; mental $r=-0.23$, $p=0.022$) showed reverse association with SF-36 scores. Moreover, PAD patients with long delay diagnosis showed significantly lower SF-36 scores (physical $r=-0.3$, $p= 0.04$; mental $r=-0.44$, $p=0.023$). Moreover there was no significant correlation between SF-36 score and time of follow up of PAD patients (physical $r=0.32$, $p=0.12$; mental $r=0.72$, $p=0.42$). It must be indicated that no significant difference between diseases were observed (Table 2).

Table 1. Patients' demographics and disease characteristics (n= 36).

Characteristics	CVID	HIgM	XLA
Number	25	3	8
Male/Female	17/8	2/1	8/0
Median age (range) year	21(15-45)	20(16-29)	19(15-32)
IgG (mg/dl)	54.21±12.4	123.48±28.3	23.5±13.9
IgA (mg/dl)	10.72±3.4	23.2±8.4	11.3±2.7
IgM (mg/dl)	6.13±1.5	132.6±17.6	16.7±9.2
$CD3^+$ lymphocyte (%)	52.4±21.5	59.3±14.2	64.43±27.3
$CD4^+$ lymphocyte (%)	34.2±8.6	33.2±7.4	36.29±13.8
$CD8^+$ lymphocyte (%)	32.4±12.7	36±13.9	34.2±17.7
CD 19^+ lymphocyte (%)	7.7±2.2	13.4±8.6	1.5±0.8

Table 2. Comparison of transformed scores of SF-36 between patients and controls.

Health dimensions	CVID	HIgM	XLA	All PAD	Controls	*P*-value*
Physical Functioning	75.8±22.8	85±13.2	73.5±3.8	76.1±25.6	90.85± 1.8	0.002
Role-Physical	59.3±4.2	25±2.5	75±3.6	58.5±3.8	77.1±2.1	0.011
Bodily Pain	69.3±23.6	49±16	72.1±20.3	68.1±22.7	83.9±3.4	0.001
General Health	37.9±17.9	23.2±16.6	42.7±20.4	37.6±18.4	71.9±1.9	<0.001
Vitality	60.2±21.6	35±13.2	59.2±25.2	57.7±22.5	68.2±2.3	0.007
Social Functioning	70.3±25.4	66.6±7.2	75±33	70.9±25.6	79.7±4.2	0.048
Role-Emotional	51.3±4.1	11.1±1.92	73.3±4.3	51±4.2	69.2±2.9	0.017
Mental Health	62.2±24.5	54.6±14	76±18.7	64.6±23	68.5±1.4	0.20
Physical Components	60.6±20.6	45.5±7	67.6±21	60.2±20.1	85.5±4.7	<0.001
Mental Components	58.8±18.3	41.8±10.9	75±19.7	59.8±19.5	72.3±3.4	0.002

* *P*-value between all PAD patients and controls

DISCUSSION

Primary antibody deficiencies refer to a heterogeneous group of disorders which are characterized by a variety of deficiencies in immunoglobulin(s) production, which affected individuals render susceptible to chronic and recurrent infectious diseases. Early diagnosis and adequate therapy are the keys for survival and a better prognosis of patients with PAD, while delays in diagnosis and/or inadequate management may lead to permanent organ damage.[16]

In this study, we used SF-36 questionnaire to assess the QoL of a group of PAD patients for the first time in our region. Moreover we used this questionnaire to verify impact of PAD diseases in long term followed-up patients. This questionnaire is one of the most widely used methods to assess health-related QoL which its framework was designed for the Medical Outcomes Study (MOS) questionnaire. SF-36 concepts has been used more than 20 years; however it is firstly published in English for comprehensive health assessments and covers eight of the most important dimensions affected by one's health state.[17] These universally valued eight dimensions are most directly affected by disease and/or treatment,[11] which can be either self-administered or interviewer administered formats. The literature on this instrument is documented by the International Quality of Life Assessment Project (IQOLA) with established reliability, validity, item internal consistency and item discriminant validity.[18,19] In this study, we used the translated and linguistically validated SF-36 QoL questionnaire.[12]

Until to now, few studies used SF-36 to evaluate the effects of IVIG therapy on PAD patients, while there is no study to apply this instrument to calculate impacts of these diseases. Eades-Perner et al performed[20] an internet-based study on the European patients with primary immunodeficiencies and showed the numbers of work/school missed days in non treated CVID patients were significantly higher than patients who received immunoglobulin replacement therapy. Eighty three percents of XLA patients showed good, very good or excellent health status by using 12-Item Short-Form Health Survey.[21] In another study, vitality, mental health, and social functioning of primary antibody deficient patients significantly improved after 10 months IVIG therapy.[22] Nicolay et al reported a significant correlation between the Life Quality Index scales and SF-36 only for the bodily pain in 47 treated patients with IVIG and also in 11 patients with subcutaneous immunoglobulin replacement.[23]

According to the results of current study, patients with PAD had reduced QoL even after long term follow-up periods. As central nervous system problems are not expected in patients with PADs, the mental health score of PAD patients did not differ from healthy controls. However, the total mental component in PAD patients was lower than control individuals in our study, due to lower social functioning score and role of emotional score of patients. In spite of regular IVIG therapy and prophylactic antibiotics, physicians must expect eventually decreased QoL in these antibody deficient patients both in physical and mental dimensions.

In contrast to different pathogenesis and severity in types of PAD, no significant changes were observed between diseases in this study, which may be due to our sample size. Nonetheless, it may suggest that better designed study is needed for evaluation of more different types of PAD with higher sample size. It could be concluded that the patients with PAD who were diagnosed timely and managed appropriately seem to have lower complications and better QoL. However, the patients with severe phenotypes and long delay in diagnosis showed lower QoL, even after medical management.

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