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Anxiety and Depression Among Patients with Predominantly Antibody Deficiencies and the Importance of Early Diagnosis

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ABSTRACT

Objective: Diagnostic delay is one of the major problems for patients with predominantly antibody deficiencies (PAD) that can lead to anxiety and depression disorders, like in other chronic diseases. We aimed to detect the frequencies of anxiety and depression in PAD patients. The second aim was to determine the influence of diagnosis delay on the patients' anxiety and depression.

Materials and Methods: In this prospective study, 40 patients and 50 healthy controls answered the Hospital Anxiety and Depression Scale (HADS). We compared the anxiety, depression, and the total scores of the patients and the healthy controls. We divided the patients into two groups as delayed and early diagnosed patients according to median diagnostic delay year and compared the HADS scores of the two groups.

Results: The anxiety, depression and the total scores of PAD patients were significantly higher compared to the healthy controls; (p=0.001, p=0.001, p=0.001), respectively. The HADS scores were significantly higher in the delayed diagnosis patient group than the early diagnosed patient group (p=0.001, p=0.003, p=0.001), respectively. We also confirmed this positive relationship between delayed diagnosis and the HADS scores with Spearman's correlation analysis.

Conclusion: We demonstrated that psychiatric disorders such as anxiety and depression are common in PAD patients, and delayed diagnosis strongly affects their anxiety and depression. Collaboration with psychologists and psychiatrists during the management of these patients may improve the quality of their life.

Keywords: Predominantly antibody deficiencies, early diagnosis, anxiety, depression

INTRODUCTION

Primary immunodeficiency (PID) is a rare and heterogeneous group of diseases, and includes more than 400 inborn errors of immunity that makes patients susceptible to frequent and recurrent infections, autoimmune disorders, allergic diseases, inflammatory diseases, and cancer. Predominantly antibody deficiencies (PAD) is the most frequent subcategory of PID disease caused by defects in B cell differentiation and antibody production. Common variable immunodeficiency (CVID) is the most common and symptomatic PID and is characterized by a reduction in immunoglobulin (Ig) G and IgA with or without low IgM accompanying a low or normal number of B cells (1,2).

Early diagnosis and treatment is the cornerstone of protecting patients from recurrent infections, and its complications. Immunoglobulin replacement therapy (IRT) decreases new infections, antibiotic use, and hospital admissions, and improves the patients' quality of life (QOL) (3-6).

The frequency of psychiatric problems related to chronic diseases varies between 10% and 30% (7). Due to the lack of awareness and suspicion among health workers and the community on PAD, the diagnostic delay is one

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of the main problems of managing these patients who are at the risk of life-threatening conditions. Despite all the improvements in medicine and early IRT, PAD patients are at the risk of both physical and psychological problems.

PID is a heterogeneous and rare disease with various clinical presentations. Various clinical presentations are also potential obstacles that cause a delay in diagnosis (8-10). Recurrent chronic infections, comorbid medical conditions, the thought and fear of having a lifelong illness, and treatment with regular follow-up can aggravate anxiety and depression, and decrease the QOL in PAD patients.

While most of the studies have investigated the QOL of PID patients, there is not much research on anxiety and depression in PAD patients (3,11-17). Several studies have shown that PAD affects both the psychosocial well-being and the QOL of the patients negatively.

With early diagnosis, patients have a chance to receive IRT that reduces frequent infections and complications. Therefore, early diagnosis and treatment improve the patients' and their families' QOL, including school, career, social, physical, psychological, and economic lives.

This study aims to investigate the anxiety and depression disorders that are usually overlooked by most of the physicians in PAD patients and compare them with healthy controls. The second aim was to evaluate the impact of the delayed diagnosis on the patients' anxiety and depression symptoms.

MATERIALS and METHODS

Patient and Study Design

In this prospective cohort study, 40 patients and 50 healthy controls were enrolled. Patients were diagnosed with PAD according to international guidelines criteria (1,2). Age, gender, occupation, marital and education status, warning signs duration, diagnosis age, anxiety and depression scores were recorded.

Data Collection

The Hospital Anxiety and Depression Scale (HADS) has been created by Zigmond and Snaith and validated by Aydemir et al. in our country (18,19). The HADS questionnaire has 2 subscales named anxiety and depression with 14 items, which also have a focus on cognitive functions. Adding both anxiety and depression scores also contribute to emotional distress monitoring (18). Each subscale consists of 7 questions, scored from 0 to 3. Total scores range from 0 to 21. The anxiety subscale cut-off score is accepted as 10 and the depression subscale cut-off score as 7 by Aydemir et al (19). This questionnaire is a valid and good predictor of anxiety and depression and easy to answer in a short time by participants, and it has been used by several investigators in different chronic diseases (20-23). The HADS questionnaire was applied to all participants to assess their anxiety and depression status.

We compared the anxiety, depression, and total scores of the patients and healthy controls. The impact of a delayed diagnosis on the patients' anxiety and depression was also investigated in the patient group. This is the first study to evaluate the effects of a delayed diagnosis on PAD patients. We accepted a median diagnostic delay of 6 years as the cut-off and divided the patients into two groups; early or delayed diagnosis. If the period from the onset of the first symptoms to the diagnosis was more than 6 years, it was classified as delayed diagnosis.

The inclusion criteria were: patients aged above 18 years and diagnosed with PAD who were currently treated with intravenous immunoglobulin 200-800 mg/kg every 3-4 weeks. The patients with secondary hypogammaglobulinemia, previous psychiatric disorders, and intellectual disability were excluded.

Ethical Issues

The Health Sciences University Gülhane Non-Interventional Clinical Research Ethics Committee approved this study (procedural number: 19/308; date: October 08, 2019). Verbal and written informed consent was obtained from all participants.

Statistical Analysis

SPSS (version 22.0, SPSS Inc, Chicago, Illinois) was used for the statistical analyses of data. Descriptive analyses were performed in determining the sociodemographic characteristics of the participants. Categorical variables were given as numbers and percentages, while numerical variables were given as mean, standard deviation and median. The Chi-square test was used to determine the association between categorical variables. We evaluated the normality of continuous variables with the Kolmogorov Smirnov and Shapiro-Wilk tests. We used the Mann-

Whitney U test to compare the anxiety, depression and total scores between patients and healthy controls. Spearman's correlation coefficient was used to compare the relationships between HADS scores, delayed diagnosis year, and age. P values <0.05 were considered statistically significant.

RESULTS

A total of 90 participants consisting of 40 PAD patients and 50 healthy controls completed the questionnaires. The sociodemographic characteristics of the patients and the healthy controls are shown in Table I. The vast majority of patients (34; 85%) had CVID, where 5 (12.5%) had agammaglobulinemia, and 1 (2.5%) had IgG subclass deficiency. Of the 40 patients diagnosed with PAD 22 (55%) were female, 22 (65%) were married, 19 (47.5%) had graduated from university, and the mean age was 36.50 ± 12.91 years. There was no statistical difference between PAD patients and controls in their sociodemographic characteristics (Table I). The current age, age of onset of symptoms, mean age at diagnosis, and mean diagnostic delay years are shown in Table II.

The median HADS anxiety, depression and total scores of the patients were significantly higher than those in the control group, respectively (p= 0.001, p= 0.001, p= 0.001) (Table III). As in the validation study, the cut-off points were accepted as 10 for anxiety and 7 for depression (19). Twenty (50%) patients had anxiety, and 23 (57.5%) had depression. Both anxiety and depression were detected in 19 PAD patients.

Delayed diagnosis of PAD affected the HADS anxiety, depression, and total scores of the PAD patients. The delayed diagnosed patients had significantly higher median anxiety, depression, and total scores than the early diagnosed patients (p=0.001, p=0.003, p=0.001), respectively (Table IV). We found anxiety in 12 (70.6%) patients and depression in 13 (76.5%) patients in the delayed diagnosis group. Of those 17 delayed diagnosis patients, 12 had both anxiety and depression. We found a significant positive correlation between the delayed diagnosis time and the HADS anxiety, depression, and total scores (r= 0.461; p=0.003, r= 0.397; p=0.011, and r= 0.441; p=0.004 respectively) but not between current age and HADS scores (r= 0.235; p= 0.145, r= 0.313; p=0.050, and r= 0.284; p= 0.075, respectively)(Table V).

Table I. Demographic characteristics of patients and healthy controls.

Characteristics	Patients (n= 40)	Controls (n= 50)	p
Age (mean± SD) years	36.50± 12.91	40.14± 7.08	0.93*
Gender, female, n (%)	22 (55)	36 (72)	0.94**
Marital Status, n (%)			0.155***
Married	26 (65)	39 (78)	
Single	13 (32.5)	8 (16)	
Widow/Divorced	1 (2.5)	3 (6)	
Education Status, n (%)			0.84***
Primary	5 (12.5)	1 (2)	
High School	16 (40)	17 (34)	
University	19 (47.5)	32 (64)	

N: Number, **SD:** Standard deviation,*Independent Samples t Test, ** Continuity Correction Chi-Square test, *** Pearson Chi-Square test.
P- values <0.05 were considered statistically significant.

Table II. Disease and time related factors of PAD patients.

	Mean (years; range)	Median (years)
Current age	36.50 (20-72)	31
Age of symptoms onset	21.33 (1-64)	19
Age at diagnosis	26.88 (2-64)	27
Diagnostic delay years	6.23 (0-26)	6

Table III. Anxiety, depression, and total scores of patients and healty controls.

Characteristics	Patients (n= 40)	Controls (n= 50)	p
HADS-A median (years; range)	10.5 (2-18)	5 (1-13)	0.001*
HADS-A ≤ 10, n (%)	20 (50)	48 (96)	0.001**
HADS-A > 10, n (%)	20 (50)	2 (4)	
HADS-D median (years; range)	8 (0-16)	3.5 (0-13)	0.001*
HADS-D≤ 7, n (%)	17 (42.5)	44 (88)	0.001**
HADS-D> 7, n (%)	23 (57.5)	6 (12)	
HADS-T median (years; range)	17.5 (3-32)	8.5 (1-22)	0.001*

HADS: Hospital Anxiety and Depression Scale, **A:** Anxiety, **D:** Depression, **T:** Total, **N:** Number, *Mann-Whitney U Test, ** Continuity Correction Chi-Square test. P- values less than 0.05 were considered statistically significant.

Table IV. Anxiety, depression, and total scores of delayed and early diagnosed patients.

	Delayed diagnosed patients (n=17)	Early diagnosed patients (n=23)	p
HADS-A median (years; range)	13 (7-18)	7 (2-18)	0.001*
HADS-A ≤ 10, n (%)	5 (29.4)	15 (65.2)	0.055 **
HADS-A > 10, n (%)	12 (70.6)	8 (34.8)	
HADS-D median (years; range)	10 (3-16)	6 (0-12)	0.003*
HADS-D≤ 7, n (%)	4 (23.5)	13 (56.5)	0.078**
HADS-D > 7, n (%)	13 (76.5)	10 (43.5)	
HADS-T median (years; range)	23 (11-32)	13 (3-27)	0.001*

HADS: Hospital Anxiety and Depression Scale, **A:** Anxiety, **D:** Depression, **T:** Total, **N:** Number, * Mann-Whitney U Test, ** Continuity Correction Chi-Square test. P- values less than 0.05 were considered statistically significant.

Table V. Correlation of HADS scores between diagnostic delay years and current ages.

	HADS anxiety scores	HADS depression scores	HADS total scores
Diagnostic delay years	r= 0.461 p= 0.003	r= 0.397 p= 0.011	r= 0.441 p= 0.004
Current ages	r= 0.235 p= 0.145	r= 0.313 p= 0.050	r= 0.284 p= 0.075

r: Spearman's correlation coefficient, P- values less than 0.05 were considered statistically significant.

DISCUSSION

In this present study, our first aim was to detect the anxiety and depression among PAD patients and compare them with healthy controls. As described in a systematic review, patients with chronic illness often have anxiety and depression symptoms due to many factors (24). We found both anxiety and depression scores to be significantly higher in the PAD group than the healthy controls in accordance with the literature (12,13). This may be the result of challenges in diagnosis, frequent infections which usually do not respond to conventional antibiotic use, inevitable complications (like bronchiectasis, cytopenias, etc.), accompanying autoimmune and/or autoinflammatory diseases and delayed diagnosis and IRT, which affect not only the physical but also the psychosocial quality of life and increase anxiety and depression in PAD patients.

There are not many studies assessing the anxiety and depression symptoms in PAD patients with the HADS questionnaire. Some researchers applied the HADS questionnaire to patients with various chronic illnesses and found lower anxiety and depression rates than in PAD patients (20-23). Camara et al. found the lowest anxiety (13.8%) and depression (16.9%) rates among patients with human immunodeficiency virus (HIV) infection in

a university hospital in Guinea (22). In the same patient group in a different country and with the same scale, Agus et al. found higher mean anxiety (15.286 ± 2.244) and depression (15.286 ± 2.244) scores than in our patients (23). In another study done by Tat, anxiety (48%) and depression (48%) rates were found to be close to our results in chronic urticaria patients. The anxiety and depression scores were also significantly higher when compared to the control group as in our study (21).

Most of the studies have determined the quality of life in PAD and a number of investigators have shown its negative impact on the patients' and their families' physical, mental, and social life (3,11-17). Tabolli et al. have hypothesized that delayed diagnosis of CVID could affect the anxiety and depression status and determined that one-third of patients (two-thirds of females) have anxiety and depression symptoms which have usually been unsuspected in the daily practice of physicians (13).

Kuburovic et al. investigated the QOL, anxiety, and depression status in PID patients and compared them with another chronic disease, juvenile idiopathic arthritis (JIA), and healthy controls. They found lower QOL in children with PID and their parents when compared to JIA and healthy controls. They also found higher anxiety and depression rates in PID patients and their parents. They also demonstrated that anxiety was higher in children and had a negative impact on QOL (12). In contrast to this study, some investigators have also made comparisons between patients with PID and other chronic diseases and found similar or higher QOL in the PID group when compared to the other chronic diseases. Similarly, QOL was lower in PID patients when compared to healthy controls (16,17,25).

Quinti et al. investigated the quality of life in CVID patients and found that CVID patients with chronic lung disease and diarrhea had decreased quality of life when compared to the controls. Quinti et al. have recommended regular follow up of the patients with chronic illnesses like patients with PAD with QOL measurements (14). Heath et al. assessed the anxiety and depression symptoms in PID patients with another scale (Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale), which has 31 questions. Contrary to our study, they showed that patients' anxiety and depression scores were not significantly high in the patients' group. However, they found that some factors like driving ability, drug administration route, family mental disorder history, hospitalization, lack of healthy food, and poor sleep had significant effects on high anxiety and depression scores (11). Delayed diagnosis is one of the main problems of managing PID that affects starting the effective treatment, complications, morbidity, mortality, other accompanying immune dysregulation diseases, and the physical, social, and mental life of the patients and their families (26). Delayed diagnosis also increases healthcare system costs and workload.

Our second aim was to investigate the impact of diagnostic delay on anxiety and depression in PAD patients. To the best of our knowledge, this is the first study to show the effects of early and delayed diagnosis on anxiety and depression and to investigate the correlation between them in PAD patients. We found significantly higher total, anxiety, and depression scores in delayed diagnosis patients. We also confirmed these findings and showed a significant positive correlation between diagnostic delay time and HADS scores. Interestingly, the median total score and the anxiety, and depression scores in early diagnosed patients were under the cut-off scores. If we compared the early diagnosis PAD patients with healthy controls, we might not find a statistical difference between the anxiety and depression scores. We demonstrated that high scores of delayed diagnosis patients cause a statistical difference between delayed and early diagnosis patients. According to these findings, we believe that early diagnosis with IRT affects the patients' anxiety and depression positively.

Aghamohammadi et al. stated that early diagnosis and immunoglobulin replacement therapy improved the patients' physical, social, and mental life and reduced complications as shown in some studies (3-6). Campell et al. have shown the positive impacts of cognitive behavior therapies (CBT) on anxiety and depression in 39 PAD patients with the HADS questionnaire. The patients' anxiety and depression scores were significantly decreased after CBT (27).

These findings highlight that anxiety and depression rates are high in PAD patients and should not be neglected. None of the PAD patients received psychological and/or psychiatric treatment before the study. We referred the PAD patients who had high anxiety and depression scores to the psychiatry outpatient clinics. Treatment of psychiatric disorders with CBT in PAD patients will help to improve the patients' lives, similar to IRT.

Study Limitations

The present study has some limitations. The first limitation of this research is that since PAD is rare and this study was conducted at a single center, it has a small sample size. We compared anxiety and depression symptoms generally in PAD patients. The results may change according to subgroups of PAD like CVID, X-linked agammaglobulinemia, IgG subclass deficiency, and hyper IgM syndrome. We did not make a comparison before and after IRT. Other factors that may affect the anxiety and depression status of patients, such as income/expense balance, job-career, family, and school problems were not investigated. Like the other physicians dealing with non-psychiatric chronic diseases, we did not make an exhaustive psychiatric evaluation before and during the treatment. If a comprehensive psychosocial assessment has not been made before the diagnosis and starting treatment, the cause and/or effect of the disorder on anxiety and depression cannot be measured even with the new advanced and disease-specific questionnaires.

CONCLUSION

Despite the advances in medicine and improved awareness of PID, delayed diagnosis is still the major problem for both patients and physicians. Challenges in the diagnosis result in a delayed diagnosis and influence the PAD patients' family life, school functioning, and physical and psychosocial conditions.

Psychiatric disorders such as anxiety and depression, similar to other chronic diseases, are also neglected when managing PAD patients. Immunologists can use instruments such as the HADS questionnaire, which is practical, valid, easily understood, and a good predictor of anxiety and depression, in their busy daily practice. Patients with high anxiety and depression scores should be referred to the psychiatry outpatient clinics for providing psychological support. Psychologists and psychiatrists must have a place in the team to help PAD patients to cope with this complex disorder.

Further prospective, multicenter, longitudinal research will help us understand the effects of PAD diseases on anxiety and depression, and improve the QOL of the patients and their families.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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