Research paper

Anxiety disorder among rheumatoid arthritis patients: Insights from real-life data

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ABSTRACT

Background: Psychiatric disorders occur in a considerable proportion of patients with rheumatoid arthritis (RA), often reflecting the difficulties of these patients in coping with a chronic debilitating disorder.
Aim of the study: To evaluate the proportion of anxiety disorder in RA patients using a large database analysis.
Methods: The study was designed as a case-control population-based study using data from the Clalit Health Services (CHS) database. Patients were defined as having RA or anxiety disorder when there was at least one documented diagnosis identified by the International Classification of Diseases-9 (ICD-9) from the medical records. The proportion of anxiety disorder was compared between RA patients and controls. A logistic regression model was used to estimate the association between RA and anxiety disorder in a multivariate analysis adjusted for age, gender and socioeconomic status (SES).
Results: The study included 11,782 patients with RA and 57,973 age- and sex-frequency matched controls. The proportion of anxiety in RA patients was higher than in controls (7.1% vs 6.3%, p=0.001). In multivariate analysis, RA was found to be independently associated with anxiety (OR 1.11 [95%CI 1.03–1.20], p=0.01).

Our study has some shortcomings, as its cross-sectional nature does not allow to make inferences about a causal relationship between RA and anxiety.
Conclusion: Our study confirms the higher proportion of anxiety in RA patients, especially young women with low SES. Physicians should be aware of such findings and, therefore, apply proper screening strategies.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by synovitis of the joints and deterioration of surrounding cartilage and soft tissue (Alamanos and Drosos, 2005). RA is a multifactorial and heterogeneous disease whose onset can be triggered by a myriad of genetic, environmental, and hormonal factors (Jalil et al., 2016; Perricone et al., 2016). RA symptoms such as joint stiffness, swelling, pain, and joint deformity are most common in the small joints of the hands and feet, but may progress to larger joints. RA is often characterized by the presence of two principal autoantibodies, rheumatoid factor (RF) and anti-citrullinated protein antibodies

(ACPAs) (Watad et al., 2014). Many of these seropositive patients suffer from diverse extra-articular presentation such as cutaneous, pulmonary and cardiovascular diseases; which increases the burden of disease. The global prevalence of RA is estimated to be between 0.5% and 1.0%, with women being from two to three times more likely to be affected than men (Suzuki and Yamamoto, 2015). RA may also involve extra-articular tissues such as lung skin, pleura and others (Turesson, 2013).

The increased prevalence of anxiety disorder in patients with chronic illnesses has been widely studied. For example, several autoimmune diseases have been shown to be associated with higher rates of anxiety (Kasama et al., 2016; Sibbitt et al., 2002; Wood et al.,

2013). More specifically, studies have investigated the comorbidity trends between RA and anxiety. Monitoring mental health status in RA patients is of central importance for improving pain management, disease treatment response and patient quality of life.

The Depression Anxiety and Stress Scale (DASS), Hospital Anxiety and Depression Scale (HADS), State Trait Anxiety Inventory (STAI), and HAQ Disability Index (HAQ-DI) have all been used to highlight the higher prevalence of anxiety and psychological distress in RA patients (Bacconnier et al., 2015; Covic et al., 2012; VanDyke et al., 2004). In one study, the anxiety level in RA patients (20–30%) was shown to be independently and longitudinally associated with the course of pain over 10 years (Odegard et al., 2007). The results of another study investigating the effects of psychological distress on arthritis pain in women showed that increased levels of anxiety predicted weekly changes in disease-associated pain (Smith and Zautra, 2008). Interestingly, persistent anxiety among patients with RA may reduce their response to treatments, with reduction in treatment effect as high as 50% as was the case with prednisolone in a recent study (Matcham et al., 2015). In contrast, the results of other studies reported average levels of anxiety in persons with RA (Anderson et al., 1988; Radanov et al., 1997). These conflicting results warrant further investigation into the association between RA and anxiety.

The observed association between the trends of RA and anxiety disorder in recent decades prompted further research. The great majority of these studies were based on a small population and many reported inconsistent results.

In order to further elucidate the complex association between RA and anxiety disorder, overcoming the shortcomings and limitations of previous literature studies, we have planned and conducted a case-control study based on data from the Clalit Health Service (CHS), the largest public health maintenance organization (HMO) in Israel.

2. Methods

2.1. Design, sample and procedures

The study was designed as a case-control population-based study using data from the CHS database. CHS is the largest healthcare provider organization in Israel, serving a population of about 4,400,000 enrollees, as of 2013. CHS has a comprehensive computerized database with continuous real-time input from pharmaceutical, medical and administrative systems. In the CHS database, the diagnoses of chronic diseases such as RA and anxiety disorder are based on data derived from hospital and primary care physicians' clinical records. These diagnoses are also validated by a systematic methodology. CHS performs the process of validation by logistic checks (such as comparing diagnoses from various providers) and by direct validation of the diagnoses of treating physicians. The validity of the diagnoses in the registry has been shown to be high (Watad et al., 2016a, 2016b, 2016c, 2015).

The control group was randomly selected from the list of CHS enrollees, excluding patients with RA. There was a ratio of 5:1 between control patients (without RA) and RA patients.

2.2. Measures

Anxiety disorder was identified by research diagnostic criteria of the International Classification of Diseases-9 (ICD-9). RA diagnosis was identified from medical records through the ICD-9 criteria, even though in Israel RA is often diagnosed according to the American College of Rheumatology (ACR) criteria. Besides the RA diagnosis, data available from the CHS database included age, gender, socioeconomic status (SES) and smoking status. In particular, SES was defined according to the poverty index of the member's residence area as defined during the 2008 National Census. More in details, the poverty index was computed based on several parameters, including household

income, education, crowding, material conditions, and car ownership, among others. It ranged from 1 to 20, based on cluster analysis, with 1 as the lowest SES and 20 the highest (Burck and Tsibel, 2013). We divided the population into 3 categories according to their SES. Smoking status was obtained by reporting the dichotomic reply (yes or not) to the anamnestic question "Do you currently smoke?". More precise details (such as the number of cigarettes per day) were not available.

2.3. Statistical analysis

Continuous variables were computed as mean standard ± deviation, whilst categorical variables as percentages, where appropriate. The proportion of the anxiety disorder was compared between patients with and without RA, using a χ^2 test for categorical variables and a *t*-test for continuous variables. Logistic regression model was used to estimate the association between RA and anxiety disorders in a multivariate analysis adjusted for age, gender and SES. All statistical analyses were performed using the open source R Statistical Software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria). Figures with p-value < 0.05 were considered statistically significant.

2.4. Ethical approval

The study was approved by the Ethical Committee of CHS, located at the Soroka Medical Center, Beer-Sheva, Israel.

3. Results

The study included 11,782 patients with RA and 57,973 age- and sex-frequency matched controls. Characteristics of the study population are presented in Table 1. The proportion of anxiety was found significantly higher among RA patients (7.1% *vs* 6.3%, p=0.001) (Table 1).

At the univariate analysis, RA was associated with several variables (being female, low SES, being aged 36–45 or 46–55 years old) (Table 2). At the logistic regression, adjusting for multiple confounding factors, being male was a protective factor for anxiety (OR 0.53 [95%CI 0.49–0.58]), whilst being old (OR 1.04 [95%CI 1.03–1.04]), having a low SES (OR 1.11 [95%CI 1.02–1.20] *versus* high SES; OR 1.09 [95% CI 1.00–1.18] intermediate SES *versus* high SES), suffering from RA (OR 1.11 [95%CI 1.03–1.20]) and smoking (OR 1.53 [95%CI 1.44–1.64]) conferred a higher risk of having anxiety (Table 3).

Table 1
Characteristics of the study population of the present study. Abbreviations: RA (rheumatoid arthritis).

Variable	Patients with RA (n=11,782)	Controls (n=57,973)	Significance (*p*-value)
Age	61.1 (± 17)	60.8 (± 17)	0.174
Gender			
Female	9103 (77.3%)	44,589 (76.9%)	Ref
Male	2679 (22.7%)	13,384 (23.1%)	0.413
Smoking status	3865 (32.8%)	16,671 (28.8%)	< 0.001
Socioeconomic status			
Low	4505 (38.3%)	22,657 (39.2%)	Ref
Medium	4816 (41.0%)	22,831 (39.5%)	0.009
High	2438 (20.7%)	12,334 (21.3%)	0.831
Anxiety	839 (7.1%)	3655 (6.3%)	0.001