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Research paper

The burden of depression in systemic sclerosis patients: a nationwide population-based study

Nicola L. Bragazzi[a,b,c], Abdulla Watad[d,e,f], Alex Gizunterman[g], Dennis McGonagle[f], Hussein Mahagna[d,e], Doron Comaneshter[h], Howard Amital[d,e,*], Arnon D. Cohen[h,i], Daniela Amital[e,j]

[a] Postgraduate School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy
[b] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, Genoa University, Genoa, Italy
[c] Centro Studi di Terapia della Gestalt (CSTG), Milan, Italy
[d] Department of Medicine B and Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel
[e] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel
[f] Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, University of Leeds, NIHR Leeds Musculoskeletal Biomedical Research Unit, Chapel Allerton Hospital, Leeds, UK
[g] The Jerusalem Mental Health Center, Jerusalem, Israel
[h] Chief Physician's Office, Clalit Health Services, Tel-Aviv, Israel
[i] Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel
[j] Ness-Ziona, Mental Health Center, Beer-Yaakov, Israel

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ABSTRACT

Background: Systemic sclerosis (SSc) can clinically present with psychological symptoms, including pain, depression, and distress about disfigurement, physical and social functioning. The existing small studies have reported a prevalence of depression ranging from 36% to 65% among SSc patients, likely reflecting the disease impact on the patient's self-image and function.
Aim of the study: To investigate the association between SSc and depression using big data analysis methods.
Methods: We designed a nation-wide epidemiological survey relying on a large database of 2500 SSc patients and explored the relationship between SSc and depression, but also the impact of depression on the survival of SSc patients. Chi-squared and *t*-tests were used for univariate analysis and a logistic regression model was used for multivariate analysis.
Results: The proportion rate of depression among SSc patients was significantly higher than controls (16.2% *vs* 10.9%), and this proportion was even higher in female SSc patients and of low socioeconomic status. At the multivariate logistic regression, SSc was found to be an independent risk factor for depression with an OR of 1.55 (95%CI 1.29–1.88, $p < 0.0001$). No significant association was found between SSc-specific autoantibodies (anti-centromere, anti-Scl-70, anti-RNA polymerase III and anti-RNP) status and the risk of depression. Depression was not found to have a significant impact on the survival of SSc patients with an HR of 1.06 (0.80–1.42).
Conclusions: This study provides further support for the high prevalence of depression in SSc patients and therefore, SSc patients may benefit from a screening approach and a broad supportive care program.

1. Introduction

Systemic sclerosis (SSc) is an autoimmune connective-tissue disorder characterized by micro-vascular damage, immunologic impairments and tissue fibrosis, due to a massive deposition of collagen and other matrix substances within the skin and internal organs (Elhai et al., 2015). According to a large, population-wide assessment of two claim databases, in the USA, SSc has a prevalence of 0.05% (Robinson et al., 2008). Immune-mediated inflammatory diseases including SSc have a substantial societal burden, owing to the impacts of chronicity, acute exacerbations and progressive disability (Enns et al., 2018).

As with other rheumatologic diseases, SSc may have prominent psychiatric features including depression, and distress about disfigurement, physical and social functioning (Amin et al., 2011;

* Corresponding author: Head of Department of Medicine `B', Sheba Medical Center, Tel-Hashomer 5262100, Israel.
E-mail address: Howard.Amital@sheba.health.gov.il (H. Amital).

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Haythornthwaite et al., 2003; Kwakkenbos et al., 2015; Malcarne et al., 2013). In particular, depression has been reported to affect anywhere between 36% to 65% of SSc patients, according to a recent systematic review of the literature (Thombs et al., 2007). Determinants of depressive symptoms in SSc patients include gastrointestinal (either upper or lower), cardiac involvement, current corticosteroid use, worse overall functional status and low socio-economic status (SES) (Bodukam et al., 2011; Nietert et al., 2005). Furthermore, depression in SSc patients correlates with poor health-related quality of life (Mura et al., 2012; Nguyen et al., 2011), as well as with disability (Del Rosso et al., 2013; Nguyen et al., 2011). Therefore, several plausible mechanisms may explain the higher proportion of depression among SSc patients including painful ulcers, the poor quality of life, immobility, constipation and many others (Del Rosso et al., 2013).

Such relevant burden of depression among SSc patients could be explained taking into account that depression is characterized by impairment and disruption of the neuro-immune axis, which control and modulate both the immune and the central nervous systems impact on human behavior (Herron et al., 2018; Hodes et al., 2015). Pathways finely tuning synaptic plasticity, neuronal activity and immune response appear to be dysregulated in depression (Wohleb et al., 2016).

However, the body of evidence linking depression and SSc is based on several small studies and the wide range of the epidemiological findings warrants further research, to clarify the complex and multifactorial relationship between SSc and mental illness. As such, the present nation-wide epidemiological survey relying on a large database, dissecting not only the relationship between SSc and depression, but also the impact of depression on SSc in terms of co-morbidities and mortality.

2. Material and methods

2.1. Design, sample and procedures

The present study was based on a very large claim database, namely the chronic disease registry of Clalit Health Services (CHS), which is the largest healthcare maintenance organization in Israel, providing service for approximately half of the population (4, 400,000 members). The CHS chronic disease registry receives input data from a variety of sources, which include pharmaceutical, medical and administrative computerized operating systems.

With the use of contemporary data-mining techniques, an array of patient data can be automatically extracted from the database, enabling wide-scale epidemiological study on a heterogeneous population in an effective manner. Using the CHS's computerized database, we were able to extract a cohort consisting of SSc patients and compared them with age- and sex-matched controls. The data drawn from the database were recorded continuously since the beginning of the utilization of computerized systems in the CHS, approximately from the year 2000 until the year 2017.

2.2. Measures

Patients with SSc were defined as such if they had at least one documented diagnosis of SSc as an outpatient, either by a primary care physician or a specialist in their medical records, or who were diagnosed with SSc in their hospital discharge papers. All SSc patients detected in the CHS database were considered eligible and, as such, enrolled in this study. Controls were randomly selected from the CHS database, with the exclusion of SSc patients. Approximately five controls were matched by age and gender for each SSc patient. Data available from the CHS database included a number of parameters, such as age, sex, SES, body mass index (BMI) and diagnoses of chronic diseases.

The SES was defined according to the poverty index of the member's residence area as defined during the 2008 National Census. More specifically, the poverty index was computed based on an array of several parameters, including household income, education, crowding, material conditions, and car ownership, among others. This composite index can range from 1 to 20, based on cluster analysis, with 1 as the lowest SES and 20 as the highest. We divided the population into 3 categories according to their SES. Concerning BMI, in order to reflect a nonlinear relation between BMI and dependent variables, BMI was broken into 4 categories: <20, 20–25, 25–30, and $>30\,kg/m^2$.

The definition of depression, similar to that of SSc, was based on a documented diagnosis of depression in medical records registered by a physician in the community or when it was listed in the diagnoses of discharge letters from a hospital. The validity and reliability of the diagnoses in the registry were found to be high, as shown in our previously published studies (Watad et al., 2017a, b, c, d).

Serum samples are routinely taken and analysed in SSc patients by indirect immunofluorescence and enzyme-linked immunosorbent assay in order to identify SSc-specific auto-antibodies during the diagnosis or the follow-up. In the present study, the following auto-antibodies were considered and assessed: namely, ANA, anti-centromere, anti-Scl-70, anti-RNA polymerase III and anti-RNP (anti-smRNP, anti-RNPA, anti-RNP68). Results of tests were considered as positive or negative in accordance with the manufacturers' recommendations. In case of multiple/serial assessment of auto-antibodies (that is to say, exams performed at different time-points during the study period), positivity was defined as having at least one exam positive on one occasion.

2.3. Statistical analyses

Rates of depression were compared between SSc patients and controls in the study sample group. The Chi-squared test was used to assess the distribution of categorical socio-demographic and clinical parameters, such as SES and gender, between SSc patients and controls, while the Student's *t*-test and one-way analysis of variance (ANOVA) or their non-parametric versions were applied for continuous parameters such as age at study production or age at diagnosis/beginning of the follow-up (between two and more groups, respectively), based on the normality of data distribution. The latter was checked using the D'Agostino-Pearson *omnibus* test.

The association between SSc and depression was evaluated by an uni-variate and a multi-variate logistic regression model, adjusting for possible confounders. Dates of registration in the medical records of SSc (or alternatively for controls, the start of follow-up), depression and death, as well as anthropometric information and medical co-morbidities, were extracted from the database, when available.

Survival analysis using Kaplan–Meier curves, log-rank test and multivariate Cox proportional hazards method was performed to detect variables associated with an increased risk of all-cause mortality, adjusting for possible risk factors.

All statistical analyses were carried out with the commercial software "Statistical Package for Social Sciences" for Windows (SPSS version 24.0, IBM, USA). Graphs were generated using the commercial software MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). Figures with a p-value less than 0.05 were considered statistically significant.

3. Results

The overall population of the present study comprised 15,141 subjects aged 63.32 ± 18.06 years (median 66 years), 2764 male and 12,377 female (female/male ratio 1:4.5): more in detail, 2431 individuals suffering from SSc were matched with 12,710 controls (case-control match 1:5.2). No statistically significant differences could be found in terms of age at study production, age at diagnosis/beginning of follow-up, gender and smoking habit (all p-values > 0.05). BMI ($p < 0.0001$) and SES ($p < 0.0001$) differed, instead, between cases and