The Burden of Various Comorbid Conditions at Initial Presentations of Systemic Lupus Erythematosus population

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ABSTRACT

Introduction: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has various manifestations among different populations.

Aim: We aimed to study the various medical comorbidities associated with SLE at the time of presentation as per Rheumatologist review.

Methods: This is a retrospective analysis using patients’ registry medical information system. All patients diagnosed with SLE were reviewed by accessing their medical records and laboratory results of investigations at the Royal hospital from 2006 to 2014. The following comorbidities were analyzed: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, lung disease, cardiovascular disease (CVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), end-stage kidney disease (ESKD), infections, thyroid disease, malignancy, and miscarriages.

Results: There were 966 patients diagnosed with SLE during the period from 2006 to 2014. The mean (SD) of age at presentation was 35.5 (11.5) years. Most patients were female (88.7 %) with mean age of 27.6 (1.4) years. Majority of the patients 786 (81.4%) were in the age group 18-45 years old, 40 (4.7%) patients were in age group 0-17years, 109 (11.2 %) patients were in age group 46-60 years, and 26 patients in age group >60 years.

At presentation, 30% had neuropsychiatry disorders, 24.5% had HTN, 19.1% hyperlipidemia, 12.2% miscarriages, 12.0 % with thyroid disease, 10.0 % CVD, 5.81 % with DM, 5 % CVA, 4.07 % CKD, 2.5 % with ESKD, 2.8 % with lung disease, 1.49% with infections and 0.53% with malignancy.

Conclusion: SLE patients have a great burden of various medical comorbidities at time of diagnosis and hence may present with CVD, stroke, CKD, ESKD and even requiring renal replacement therapy at initial encounter with health-care professionals. Strengthen health system at primary level and education of public and health work force is the main challenge to further reduce the risk of these comorbidities and the consequences.

Keywords: Systemic lupus erythematosus, Lupus erythematous, Comorbidities, Diagnosis, Diseases burden

Introduction

Health inequalities are defined as "differences in the incidence, prevalence, mortality and burden of diseases and other adverse health conditions that exist among specific population groups" (National Institutes of Health [1]. Among rheumatic diseases, systemic lupus erythematosus (SLE) has one of the uppermost health discrepancy rates between populations and even among certain groups of a population [2-4] and as per LUMINA cohort, it is a disease that more severely affects disadvantaged minority population groups [5]. Hence, SLE is a complex chronic autoimmune disease with variable clinical presentations, with complex interaction and association with socioeconomic and demographic features, that is characterized by fluctuating disease activity and multiorgan involvement [6,7].

Epidemiological studies on the prevalence of SLE show a wide
range across different racial populations (21.7 to 124 per 100,000 population), that possibly related to variability in genetic and environmental factors [4,6,8]. The disease may present with acute, severe, and serious symptoms, or present as a fluctuating and chronic process that impacts several systems [7]. Lately, the survival of SLE patients had increased because of improved awareness, early diagnosis, augmented immunosuppressants and better-quality management of associated complications [4,8,9]. This improvement highlights the importance of treating comorbidities that accompany the disease or its treatment [7,9,10]. Furthermore, the known comorbidities that are associated with the disease itself and the side effects of therapy are considered as independent risk factors for morbidity and mortality [7].

SLE is categorized as a "B-cell disease. The flowing and floating lymphocytes in the blood of SLE patients show a Th2-similar form; however, Th1 lymphocytes and interferon (IFN)-γ have been verified to be an imperative for SLE pathogenesis [7,11-14]. However, chemokines and cytokines, such as interleukin (IL)-6, B lymphocyte stimulator, IL-17, type I IFNs, tumor necrosis factor (TNF)-α, and Th1 chemokines play central role in the pathogenesis of SLE. These cytokines and or chemokines are important in the arrangement, development, distinction, and initiation of several immune competent cells, that facilitate the indigenous inflammation and yield the tissue damage and injury at numerous body organs [7,11-14]. SLE causing damage that is defined as "an irreversible change in an organ or system that has occurred since the onset of SLE" [15-19]. The management of patients with SLE is aimed not just at instantaneous control of disease activity, but also at the preclusion of organ damage from various treatment modalities and associated comorbidities [6,15,20-23]. These damages of various end organs may be subtle at initial presentations but tend to progress, unless managed appropriately by multidisciplinary team of specialized clinicians [15]. In addition, studies among middleeast populations are rare, and hence we conducted this study to know the pattern and comorbidity at the time of diagnosis of SLE.

Materials and Methods

This cross-sectional, of one single evaluation of each patient that was based on data collected from Oman health information system (alshifaa system) which was launched in 2006. The Royal hospital (RH) is the main tertiary care hospital for rheumatology, majority of SLE patients are referred to RH from different parts of the country for clinical diagnosis, laboratory investigations and management. SLE diagnosis was based on the American College of Rheumatology classification criteria; ACR97; (which includes the clinical manifestation and laboratory evidence) [24]. Rheumatologist reviewed all these cases at time of diagnosis. To assure all enrollee fulfilled accurate diagnostic criteria, all laboratory tests for autoantibodies were reviewed to cross reference with the ICD classifications as obtained from medical records.

The following comorbidities were analyzed: diabetes mellitus (DM), hypertension (HTN), hyperlipidemia, lung disease, cardiovascular disease (CVD), cerebrovascular accident (CVA), chronic kidney disease (CKD), end-stage kidney disease (ESKD), infections, thyroid disease, malignancy, and miscarriages. Demographic parameters (age and gender), the different co-morbidities, medications used, and laboratory data were collected from the systems for each patient at time of initial encounter. Stata for Windows (version 13) was used for statistical analyses.

Results

There were 966 patients diagnosed with SLE during the period from 2006 to 2014. Mean (SD) age at presentations was 35.5 (11.5) years. The majority of patients were female which constitute 88.7 % of the total SLE patients) with mean age 27.6 (1.4) years.

Majority of the patients 786 (81.4%) were in the age group 18-45 years old (Figure 1), 40 patients (4.7%) in age group 0-17 years, 109 (11.2 %) patients were in age group 46-60 years, and 26 patients in age group >60 years.

At presentation, 24.5% had HTN, 19.1% hyperlipidemia, 12.2% had miscarriages, 12.0% had thyroid diseases, 10.0% CVD, 5.81% with DM, 5% CVA, 4.07% CKD, 2.8% with end stage kidney disease (ESKD), 2.5% with lung disease, 1.49 % with infections and 0.53% with malignancy, as shown in Table 2 and Figure 2.

Neuropsychiatric disorders including seizure, stroke, psychosis, mood and cognitive disorders, were present in 30% in patients at initial SLE presentation.

Discussion

The present study showed that patients having significant proportion of medical comorbidities at the time of diagnosis with SLE, with a mean age of 35.5 (11.5) years. The majority (almost 90%) were young females with an average age of 27 years. Patients were suffering from various clinical manifestations and medical comorbidities with many laboratory abnormalities. These include DM, HTN, thyroid disorders, hyperlipidemia and end organ dysfunction such as CKD, CVA and CVD. These comorbidities at time of diagnosis may be a manifestation of various genetic, environmental and socioeconomic factors [25-28].

Reviewing studies from the same regions revealed similar female to male ratio of 9:1 in a Saudi study. Their mean age (±SD) were 25.3±10.5 for male and 28.5±10.9 years for female, with highest occurrence in the 20–30-year age group [29]. In Kuwait, a study reported 98 females and 10 males diagnosed as SLE, with a median age of 31.5 years [30] and another study from Lebanon of 86 females and 14 male's patients with SLE, reported a median age of 26 years [31].

Internationally, the RELESSER Registry, which is a Spanish Nationwide Study, reported a median age of 34.6 years [32]. Others found that among 4,863 residents of British Columbia, Canada, with SLE, 86% were female with mean age of 48.9 years [33]. They reported the age-, sex-, and entry time-matched hazard ratios (HRs) for myocardial infarction (MI), stroke, and CVD were highest during the first year after SLE diagnosis: 5.63 (95% CI 4.02-7.87), 6.47 (95% CI 4.42-9.47), and 6.28 (95% CI 4.83-8.17), respectively [33]. McCormick et al. [34] found that even years before diagnosis, SLE patients incur significantly elevated direct medical costs compared with the age- and sex-matched general population, for hospitalizations, outpatient care, and medications.

The present study found that almost six percent of patients have DM at the time of diagnosis of SLE. The co-existence of DM and SLE is a well-known phenomenon [35-37]. Chronic inflammation and oxidative stress in SLE may contribute to insulin resistance as part of autoimmune disorder, which is a significant module of DM [38,39]. Anti-insulin antibodies and chronic inflammation were
associated with hyperinsulinemia and insulin resistance and may account for the development of DM in SLE patients [40-42]. An animal mouse model of SLE suggested with insulin resistance and dysglycemia [43]. A recent study found that SLE group bi-hormone dysglycemic abnormality with amplified insulin resistance and high glucagon serum level in spite of normal glucose tolerance, preserved skeletal muscle GLUT-4 translocation and normal beta cell function [44]. Furthermore, SLE patients who are nondiabetic have signs of reduction in sensitivity to insulin [38]. Similarly, these non-diabetic patients have an increase prevalence of the metabolic syndrome up to an almost one fifth [38]. Later, as SLE progress and managed, insulin resistance and the adverse effects of immunosuppressive therapy might worsen the diabetes and its complications. Finally, SLE patients would have at least 5-fold higher risk to develop DM [40,42].

In the present study, one quarter of participants had high BP at initial presentation and diagnosis of SLE. HTN is highly co-exist among SLE population, and the immune system autoimmunity is a crucial aspect in the HTN development in laboratory-mouse-model of SLE [45-47] and that neuroimmune pathway has possible importance in the HTN development and kidney injury [45-47]. Researchers found that impaired kidney hemodynamic function, peripheral vascular function, amplified oxidative stress, and changed inflammatory cytokine production contribute to HTN in a well-known laboratory-mouse-model of SLE and hence, the autoreactive B cells and pathogenic autoantibodies mechanistically lead to the HTN pathogenesis in SLE [45,46]. They concluded that adaptive immune system dysfunction associates with HTN and that both specific activating autoantibodies and circulating antibodies to nuclear antigens correlate with BP rise in SLE patients [48,49] and suggested that creation of autoantibodies by plasma cells mechanistically leads to autoimmune-associated hypertension. Arterial HTN is reported to burden the majority of SLE patients, especially with disease progression, and contributes significantly to augmented rise of atherosclerosis and hence increased CVD risk [50]. Therefore, research data suggest that SLE population have an increased CVD risks, recommending stringent and strict BP tight control of top priority management strategy SLE population [50].

Atherosclerosis is more frequently noted in the elderly general population whereas young women are normally group free from atherosclerosis, in part because of the protective effects of estrogen. However, in SLE, young women have increased-incidence of CVD, which is ascribed to SLE itself. In addition, hyperlipidemia, hypoalbuminemia and high blood pressure along with hypercoagulable state and associated vasculitis all play additive risk in rising the morbidity risk of CVD. In the present study, hyperlipidemia was present in almost one fifth of participants at the time of SLE diagnosis. This is in support of reported risk of atherosclerosis occurring more often among SLE patients than in the general population and advances more rapidly especially if inflammation is not well controlled [51].

Lupus patients have a higher burden of traditional CVD risk factors compared with the general population, a risk that is 2 to 10 times that of the general population, with a greater increase in relative risk generally observed in younger patient groups traditional CVD risk factors [4,52-54]. The global prevalence of CVD events in RELESSER Registry cohort was 7.4% since SLE diagnosis [55-58] and 7% in the LUMINA cohorts [59,60]. However, our study reported a higher percentage of 10% even at initial presentation at time of diagnosis. This is consistent with other European [55,58] and American cohorts [5,58,60], the frequencies of which ranged from about 9.0% to almost 20.0%. This supports the fact that lupus patients have a higher risk of accelerated atherosclerosis, comparable to that of diabetes patients, even, after controlling for traditional risk factors, individuals with SLE are at increased risk for CVD when aortic stiffness was evaluated by MRI [61]. Inflammation and autoimmune disorders seems to play an important non-traditional risk factor for CVD [62-64]. In some patients with lupus, MI may develop even before the diagnosis of SLE or shortly thereafter, suggesting that there may be a link between autoimmune inflammation and atherosclerosis [13].

The Hopkins Lupus Cohort reported that the utmost significant demographic-predictors of damage-progression were diagnosis at older age, race, ethnicity and low income [65,66]. Low income causing malnutrition, limited access to quality care and poor compliance with medication were reported as the socioeconomic status variable associated with high risk for CVD among SLE population [66]. The increased risk of progression of SLE in non-Caucasians could be attributed to by other risk markers such as income, high blood pressure and urinary protein [65]. Furthermore, researchers of Disease activity (SELENA-SLEDAI) reported a higher degree of damage progression [21,24,67,68].

End organ damage can be enhanced by co-existence of several predisposing factors. In our study, SLE patients have other risk factors for development of CKD including diabetes, hypertension and hyperlipidemia [69-71]. Jiang et al. [69] concluded that SLE population diagnosed with DM has a significantly higher risk to develop ESKD. In our study almost 7% have CKD and ESKD at initial presentation. It has been reported that around 10% to 30% of patients with severe lupus nephritis end up with ESKD within 15 years of diagnosis [72]. In developed countries, the 5, 10, and 15years incidences of ESKD in patients with lupus nephritis were reported as 11%, 17% and 22%, respectively [73]. A prospective cohort study demonstrated that insulin resistance was associated with a rapid decline in kidney function and SLE patients with DM may represent higher insulin resistance and more comorbidities, which predisposes them to develop ESKD [69,71].

In the present study, neuropsychiatry disorders were present in 30% at time of initial presentation of SLE. The occurrence of neuropsychiatric appearances varies regionally and internationally world-wide [2,29-31,74]. Regionally, studies from Saudi, Kuwait and Lebanon reported neuropsychiatric disorders in 26%, 23% and 19%, retrospectively. These findings are lower than what we reported. The diagnosis of, especially primary, manifestations are difficult, as both focal and diffuse manifestations may occur primary. Many researchers have labeled autoantibodies and cytokines as possible mediators, affected cerebral vasculature, and/or interfering with neuronal connectivity [7,14]. International inception cohort by Hanly et al. [75] reported a 28% of SLE patients suffered at least 1 neuropsychiatric manifestation about the time of diagnosis and the existence of neuropsychiatric manifestation was linked with decreased quality of life and augmented organ damage [75]. A meta-analysis study found that CNS findings included: headache (12.2%), mood disorders (7.4%), seizures (7.0%), cognitive dysfunction (6.6%), and cerebrovascular disease (5.0%) and other syndromes arisen in less than 5% of the SLE population [74].
Our data showed that there is quite a high risk of infections and malignancy at time of diagnosis of SLE. The Spanish Rheumatology Society Lupus Registry studied a total of 3658 SLE patients and found that a total of 705 (19.3%) patients suffered ≥1 severe infection [32,57,58]. Also, they found that the time from first infection to second infection was significantly shorter than time from diagnosis to first infection (p < 0.001). They reported that respiratory infections were the most common (35.5%) but bloodstream infections were the most frequent cause of mortality by infection (42.0%) [32,57,58].

Cao et al. [76] analyzed 59,662 SLE patients, where malignancy was associated with SLE with higher incidence of lymphoproliferative and leukemic cancers, as well as and some non-hematologic malignancies and thyroid malignancies. They reported that the pooled RRs were 1.28 (95% CI, 1.17–1.41) for global cancer risk [76]. A multisite international SLE cohort concluded that there is small increase in risk of cancer overall in SLE compared to general population, but this risk is in early life even in childhood group [77-79] and risk would be further increased as these patients enter adulthood life and with disease progression.

The present study found that 12% of participants have thyroid disease at initial time of SLE diagnosis. A study from Kuwait found that subclinical hypothyroidism was present in13.3% of SLE patients and all were females. They found that overt hypothyroidism was present in 8.3% of SLE patients whereas biochemical hyperthyroidism was seen in 5% of SLE patients. They reported euthyroid sick syndrome in 16.7% of SLE patients and thyroid autoantibodies in 18.3% of SLE patients [80]. A study retrospectively analyzed in 1,006 Chinese SLE patients reported subclinical hypothyroidism in10.04% compared to 0.91–6.05% in general population. lupus nephritis (LN) was associated with higher incidence of subclinical hypothyroidism (13.4%) in SLE with LN vs 7.3% in SLE without LN (P < 0.001) [81]. In multivariate analysis in a case-control study, SLE was associated with hypothyroidism (OR = 2.644, 95% CI, 2.405–2.908) [82]. Five thousand and eighteen patients with SLE and 25,090 age- and sex-matched controls were evaluated for thyroid dysfunctions. The risk of hypothyroidism in SLE patients was increased with respect to the prevalence in controls (15.58 and 5.75%, respectively, P < 0.001) [83].

The respiratory system can be affected by the inflammatory process of SLE, where the pleura, airways, parenchyma, vascular, and respiratory muscles could be involved [84-87]. The prevalence of various respiratory abnormalities varies among populations and races [88,89]. Pleuritis was present in 45% of patients with chronic SLE and in 3% of the initial manifestations [50,87,90,91]. Also, it has been reported that sterile pleural effusion and pneumonia, which is usually due to infection are the most common respiratory manifestations in SLE patients [56,85-87]. In addition, interstitial lung disease (ILD) occurred in variable number depending on duration of SLE but about 3% to just below 10% of patients tend to be symptomatic [87,92,93], they are found more commonly in late-onset SLE [94], where the rates are more than doubled [87,92-94] and could be even associated with malignancy [93]. However, lung function studies, have revealed an increase of abnormalities even in the absence of clinically apparent lung disease or by high resolution CT scan [95]. Furthermore, researchers even reported other manifestations such as volume restriction, decreased compliance, reduced diffusion capacity, and hyperventilation with arterial hypoxia at rest or during exercise [96]. In addition, myopathy may lead to dysfunction of the diaphragm and other respiratory muscles in patients with SLE [84,87,97]. The present study found that pulmonary lung disease occurred in 2.5% of SLE patients at time of initial presentation. This is a modest percentage but with longitudinal follow up for a decade or more it would increase significantly if the inflammatory process is not adequately controlled, as recent studies implicated plasma IL6 in the development of pulmonary manifestations and its importance in the pathogenesis of local inflammation and tissue damage [7].

SLE, both lupus nephritis and anti-phospholipid antibodies, increases the risks for maternal hypertension and premature births [98]. In the present study, miscarriages was present in 12.2% of participants at the time of diagnosis of SLE. However, the risk of miscarriage may be dependent on disease duration and various organ involvement [98], a study of the rate of pregnancy loss in patients with active nephritis was reported to be as high as 60% [99], but recent data have shown improved outcomes, including recently quoted live birth rates in majority of pregnancies [100].

The results of this study are limited by the retrospective analysis of data that was dependent on the accurate entry and coding of patient data into the alshifaa databases, which was collected prospectively.

Although retrospective studies might under estimate the frequency of events, some of these differences are likely due to varying definitions of certain comorbidities, such as CVD events, and due to observation times, our prevalence nonetheless remained relatively high compared to other studies as discussed above. This frequency of comorbidities in our patients presented a high frequency of traditional and non-traditional risk factors, particularly DM, high BP and hyperlipidemia.

Another important limitation concerns the etiologic attribution of events. CV events in SLE, particularly heart failure and rhythm disorders, can be the result of several causes, such as lupus activity, fluid overload, anemia, and others. Nevertheless, in daily clinical practice, it is often not possible to establish the exact etiology of some CV event because of the concurrence of more than one pathogenic mechanism in the same patient.

A further limitation of our study was that we did not include important traditional risk factors, such as obesity, sedentary lifestyle and use of steroids. However, none of our female patients were ever smoker and only few men were smokers. Furthermore, we did not consider 2 subgroups of diabetes (ie, types 1 and 2 diabetes), which in the context of SLE could be totally different.

Finally, the strengths of the present study that it’s the only center of all MOH in Oman that do all the laboratory investigations especially the autoantibody screen and hence capture almost all patients. However, another hospital managed SLE cases but with limited number as an educational institute and may be less than 10% of cases [101-104]. In addition, there may be some missing data for potentially confounding variables.

Conclusion

This study identified various clinically relevant comorbidities that may warrant careful consideration in patients’ clinical management. Early risk stratification of various medical comorbidities at diagnosis should be incorporated into the management of SLE, with goal of protecting whole organs of SLE patients against inflammation, as the disease wane and wax through its natural progression process in association of various postnatal environmental risk factors.
These numerous potentially adjustable risk factors for damage accrual with an integrated and unified approach to manage SLE disease activity contributing to every organ dysfunction. However, with advancement immunosuppressive medications and multidisciplinary team approach management and support, the long-term outcome of these comorbidities is usually favorable.

References


