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Systemic lupus erythematosus: An update for ophthalmologists

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ABSTRACT

Systemic lupus erythematosus (SLE) is a life-threatening multisystem inflammatory condition that may affect almost any part of the eye. We provide an update for the practicing ophthalmologist comprising a systematic review of the recent literature presented in the context of current knowledge of the pathogenesis, diagnosis, and treatment of this condition. We review recent advances in the understanding of the influence of genetic and environmental factors on the development of SLE. Recent changes in the diagnostic criteria for SLE are considered. We assess the potential for novel molecular biomarkers to find a clinical application in disease diagnosis and stratification and in the development of therapeutic agents. We discuss limited forms of SLE and their differentiation from other collagen vascular disorders and review recent evidence underlying the use of established and novel therapeutics in this condition, including specific implications regarding monitoring for ocular toxicity associated with antimalarials.

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1. Introduction

1.1. *Systemic lupus erythematosus and the ophthalmologist*

Systemic lupus erythematosus (SLE) is a life-threatening multisystem autoimmune disease. Around a third of patients may have ocular involvement, ranging from relatively mild manifestations to severe, sight-threatening disease. The role of ophthalmologists in the care of these patients ranges from contributing to the acute care of a patient with severe active disease to the longer-term management of complications arising from the disease or related to its treatment.

1.2. *Update on epidemiology and global impact*

1.2.1. *Worldwide incidence and prevalence*

The incidence and prevalence of SLE shows great variation worldwide. In their 2011 review, Senga and colleagues report annual incidence rates ranging from 0.3 to 8.7 per 100,000 per year and prevalence ranging from 1.1 to 534.9 per 100,000, with the highest incidence occurring in the USA, Caribbean, Brazil, and Sweden. SLE is generally less common in Europe and Asia.[A] In Europe, Caspard and colleagues reported an epidemiological study for England from 1998 to 2010, noting an annual incidence of 5.5 per 100,000 per year.[B] In a US study analysing 34,339 SLE patients with Medicaid coverage, Feldman and colleagues reported an incidence of 23.2 per 100,000 per year and a prevalence of 144 per 100,000. This study found an unusually high prevalence and incidence that is likely to reflect the nature of the inclusion criteria (i.e., limited to Medicaid users) and is discussed later in this review in the context of the influence of social deprivation.[28] In contrast, two state-based studies, the Georgia Lupus Registry[72] and the Michigan Lupus Epidemiology and Surveillance Program,[127] identified potential cases from a wider range of sources, albeit over narrower geographical areas. The overall age-adjusted incidence rate was 5.6 per 100,000 per year for the Georgia Lupus Registry and 5.5 per 100,000 per year for the Michigan study, with an age-adjusted prevalence rate of 73 per 10,000 reported for both studies. These studies all confirm that black race or ethnicity is associated with higher incidence and prevalence with this difference being most marked in women (see the following sections).

1.2.2. *Influence of gender*

SLE predominantly affects females of childbearing age, with only 4%–22% patients being male. Feldman and colleagues' study found that SLE prevalence was over 6 times higher in women (192/100,000 for women vs 32/100,000 for men).[28] The Georgia Lupus Registry reported age-adjusted prevalence of 128/100,000 for women versus 15/10,000 for men, and the Michigan Lupus Epidemiology and Surveillance Program reported 129/100,000 for women and 13/100,000 for men.[72,123] As alluded to earlier, the highest risk group in all these studies are black women, with a prevalence of 286/100,000 in the Feldman study, 196/100 000 in the Georgia study, and 186/100,000 in the Michigan study.

The extent to which there is a distinct male lupus syndrome remains controversial. Some have reported a higher disease activity at presentation,[96] with others suggesting that men with SLE have a more aggressive course,[133] but a careful review of the literature by Murphy and colleagues determined that these studies often lack correction for confounders such as ethnicity or age and that overall there are limited data available for a negative prognostic association between male gender and disease activity or mortality. They do, however, agree that differences in system involvement between the sexes may be seen, with men being less likely to be affected by musculoskeletal symptoms, photosensitivity, oral ulcers, and retinopathy than women.[59,97]

1.2.3. *Influence of age*

Late onset SLE (>50 years) appears to run a milder course compared to childhood onset SLE[C] (<18 years). Simmons and colleagues analyzed the influence of ethnicity and gender changes according to age of onset, with the female bias increasing across age groups.[C] Late onset SLE is particularly associated with the clinical features of pulmonary involvement and serositis. It is also more commonly associated with positive rheumatoid factor and antinuclear antibody, but the significance of this is unclear because these serological markers are also more common in the non-SLE elderly population. Even though late onset SLE is associated with poorer survival, this is likely to be due to the interaction of inflammation and ageing increasing atherosclerosis.[6] In contrast to the milder course of late onset SLE, childhood onset SLE is aggressive with a higher prevalence of renal and neurologic involvement and irreversible damage.[D] Anti-RNP positivity, anti-Sm positivity, and a low CH50 (50% hemolytic complement) are more common in early than late onset SLE.[6]

1.2.4. *Influence of social deprivation*

In addition to the established influences of ethnicity, gender, and age, social deprivation appears to be a risk factor for SLE. In their socio-demographic analysis of Medicaid enrollees in the US, Feldman and colleagues found significant differences according to socioeconomic status with the highest prevalence in the lowest socioeconomic status quartile (prevalence of 168/100,000), a difference that persisted even adjusting for age, sex, and race or ethnicity. They comment that the Medicaid group is a "high-poverty group, with significant racial and ethnic minority representation." It is likely that these 2 factors account for the higher incidence and prevalence seen in this cohort compared to most previous US studies.[28]

1.2.5. *Socioeconomic burden*

SLE can have a substantial effect on the quality of life of the affected individuals. The 2013 Lupus European Online survey which was completed by 2,070 European patients, detected that nearly 70% of patients felt the disease had affected their careers, with 27.7% changing careers within 1 year of diagnosis. The main complaint was reduced productivity as a result of fatigue (82.5%), with decreased ability to plan affecting all areas of daily life.[42] This decrease in productivity can lead to employment loss within 3.7 years from diagnosis