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Review

Gender balance in patients with systemic lupus erythematosus

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ABSTRACT

Factors are reviewed that contribute to the contemporary view of a disproportionate prevalence and incidence of SLE in females. Recent studies on the epidemiology of SLE report that global incidences and prevalences of SLE for Caucasian and Black populations are of the order of 5.5 and 13.1 per year and 81 and 212 per 100,000 persons respectively. Both parameters displayed age dependent variation over a 90-year lifespan. The female to male (F:M) incidence of SLE varied with age, being approximately 1 during the first decade of life, followed by a sharp increase to 9 during the 4th decade, thence declining in subsequent decades before an increase during the 7th or 8th decade. A cognate review of SLE diagnosis in neonates revealed a F:M ratio of ≈1.2, consistent with the epidemiology review and the sporadic nature of SLE. Notional estimates of disease duration showed a steady increase from a base level for both males and females. The linear trend line for males was always lower than the trend line for females, supporting clinical experience that SLE is a more severe disease in males. Over a 14-year interval ending in 2012, the notional duration of SLE increased from 10–15 years to 20–25 years, probably reflecting advances in diagnosis and clinical practice.

A metastudy of SLE concordance in twins revealed a 75% discordance in monozygotic twins compared to a 95% discordance in dizygotic twins confirming the importance of environmental factors in susceptibility to SLE. The elevated discordance in dizygotic SLE twins (and between siblings) suggests a role for the intrinsic genomic sexual dimorphism due to divergence of Y chromosome regulatory loci from their X chromosome homologues due to lack of recombination of mammalian sex chromosomes over evolutionary time.

Estimates were made of the incidences of SLE in males and females based on population data for nine autosomal deficiency loci of major effect, plus expected male prevalence associated with Klinefelter's syndrome and female prevalence associated with Triple X syndrome. These genetic abnormalities accounted for ≈4% of female and ≈23% of male Caucasoid prevalence and for SLE resulting in a F:M ratio of ≈0.17. It may be deduced therefore that the impressive preponderance of SLE in females arises from a combination of environmental triggers and susceptibility loci of relatively small effect acting between the interval from the mini-puberty of childhood to the peak of reproductive adulthood. It is in this cohort of females, and especially in the Black population, that combinations of loci of minor effect acting together with environmental factors initiate defective apoptosis resulting in consequential autoimmune disease especially SLE. We postulate that because apoptosis is itself a very complex process, and defective apoptosis is an important contributor to SLE, there will be many combinations of susceptibility loci and environmental stimuli that can result in SLE (and other autoimmune disease(s)), of varying severity.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease characterised by the presence of autoantibodies against chromatin, including dsDNA, and inflammation of various organs, especially the kidney and skin (recent reviews [1,2]). For many years SLE has been considered an archetypal hypersensitivity state mediated by inflammatory processes following organ specific deposition of immune complexes with consequential activation of inflammation pathways including the complement system [2]. The disease is managed by anti-inflammatory and immunosuppressive therapies that significantly reduce mortality rates, but do not effect cures [3]

The aetiology of SLE is unclear, however ineffectual clearance of cellular debris and chromatin during apoptosis has been proposed as the important effector mechanism in many instances and there is considerable evidence to support this hypothesis (reviewed by [4]; and [5,6]). The incidence of SLE is sporadic, however familial disposition is well described and is often associated with known deficiency states. The latter include deficiency states in the early acting components of the classical complement pathway [2] and TREX1 activity [7,8].

The overall observed and widely reported gender imbalance in persons diagnosed with SLE is impressive. As estimated in this report, ≈9 females are diagnosed with SLE for every male, although as will be seen this ratio varies between ethnic populations and with age of the test population. It is proposed the extraordinary preponderance of SLE in females of reproductive age provides important clues to the underlying triggers that lead to SLE in susceptible persons. This review will seek to identify those factors that contribute to the disproportionate prevalence SLE in females.

2. Incidence and prevalence of SLE in human populations

There have been many reports of the incidence and prevalence of SLE in diverse human populations. These studies have shown higher prevalences in women of reproductive age (20–40 years) and in women of Black or Asian ancestry (reviewed by [9,10]). Virtually all studies report an impressive female to male (F:M) ratio. Estimates used in this review of incidence and prevalence of SLE for Caucasoid and Black populations are based on the studies of [11,12] because they discriminate clearly between these two ethnic populations. Mean incidences and prevalences of SLE for Caucasian and Black populations are 5.5 and 13.1, and 81 and 212 per 100,000 persons respectively. The F:M ratio is 9 for both ethnic groups. Data are also included of estimates from two very recent European studies of ethnically mixed populations from the United Kingdom (UK) [13] and France [14]. A fifth report [15] includes data for a small population of indigenous Australians. A summary of the prevalence and, incidence rates and F:M ratios from these studies is shown in Table 1. It is in the nature of epidemiological research that results are sensitive to the methods and definitions used. Differences between the four reports summarised in Table 1 reflect variations in database composition and disease definitions as well as the composition of the populations interrogated together with any environmental factors that may be involved. Despite these limitations, a consistent epidemiology of SLE emerges.

Both incidences and prevalences are higher for females than for males, and the increased susceptibility of individuals from African descent for SLE is clearly apparent. It is interesting to note that the higher incidence and prevalence rates of SLE reported by Bossingham, D. [15] for indigenous Australians in North Queensland are similar to those for European and North American individuals from African descent. Given the long isolation of indigenous Australians, this observation very likely reflects their more closely shared African genetic ancestry.

The gender imbalance ratio based on prevalences is ≈10 for all studies. The data of Rees and Arnaud [13,14] included variation in both incidence and prevalence rates as a function of age by decade and it seems clear that SLE may be newly diagnosed in all decades of life. The pronounced increase in incidence of SLE in females between 20 and menopause is clearly seen and contrasts with the slower but steady increase in male diagnosed SLE over their lifetimes. These observations translate into highly variable F:M ratios based on incidences (and prevalences) over a life time and probably account for the variation in ratios often reported in the literature. There are two peaks in the F:M ratio based on incidences – these occur in the third decade (20–29 years) due the increased susceptibility of females of reproductive age and again in persons older than 79 years. A simplistic measure of disease duration (in years) is the ratio of prevalence to incidence. We have used the data of Rees et al. [13,16] to show this graphically in Fig. 1 for both males and females.

Fig. 1 shows that over a human lifetime disease duration is shorter in males than in females which is consistent with the many reports that conclude that SLE is more severe in males and especially in children [17–19]. The steady increase in disease duration over adulthood likely reflects less severe disease profiles and rapid improvements in the diagnosis and treatment of this disease with consequent increased longevity. This point is reinforced by Rees et al. [13] who estimated temporal incidences and prevalences for their mixed UK population over the interval 1999 to 2012. Disease duration estimates for these data are presented in Fig. 2 and show a steady increase in disease longevity.

Table 1
Meta-analysis of incidence and prevalence of SLE per 100,000 person years from 4 seminal studies and 1 Australian study.

Data source		Caucasians		Black		Overall	
	Gender	Incidence	Prevalence	Incidence	Prevalence	incidence	Prevalence
[12]	Females	6.3	86.7	12.8	186.3	9.3	127.8
	Males	1.2	8.7	2.1	19.3	1.6	12.4
	F:M ratio	5.3	10.0	6.1	9.7	6	10
[11]	Females	4.7	59	13.4	196.2	9.4	131.1
	Males	0.7	7.5	3.2	23.7	1.7	14.9
	F:M ratio	6.7	7.9	4.2	8.3	6	9
[14]	Females					5.51	79.1
	Males					0.92	11.83
	F:M ratio					6.0	6.7
[13]	M & F	6.73	134.53	22.5*	247.62*	8.34	167.62
						1.44	24.82
	F:M ratio					5.8	6.8
[15]			30.2**		92.8		45.3
(Aust. indigenous)	F:M ratio		6.5**		5.5		6.2

*Average from Black African, Caribbean & other. ** Estimated from data includedin paper. Grey shaded boxes represent non-available or not applicable data.