

Systemic Lupus Erythematosus: some Epidemiological and Clinical Aspects

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Abstract Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with a wide array of clinical manifestations including rash, photosensitivity, oral ulcers, arthritis, serositis, glomerulonephritis among others clinical findings. In this paper we globally summarized the most important epidemiological and clinical aspects to bear in mind, when the time comes to make the diagnosis of this rheumatic disorder and its management. Factor that are involved in the SLE pathogenesis and novel treatment options are mentioned.

Keywords: *systemic lupus erythematosus, epidemiology, prevalence, incidence, mortality, immunology*

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1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder which develops in genetically prone individuals under the influence of various environmental factors. It is a prototypical autoimmune disease with a wide array of clinical manifestations (rash, photosensitivity, oral ulcers, arthritis, pleuritis, pericarditis, kidney problems, seizures and psychosis, blood cell abnormalities). It is characterized by the production of antibodies to components of the cell nucleus [1,2]. Primarily a disease of young women; occurs from infancy to old age, with peak occurrence between ages 15 and 40. Females are affected far more than males (6-10:1); and blacks (and possibly Hispanics, Asians, and Native Americans) are affected more than whites [1,2].

Although there is a strong familial aggregation, the disease is relatively uncommon and most cases are sporadic. The condition may occur with other autoimmune conditions (e.g., thyroiditis, haemolytic anaemia, idiopathic thrombocytopenia purpura) [1,2]. Diagnosis can be very difficult. The gold standard is a rheumatologist's diagnosis. The American College of Rheumatology (ACR) uses a standard classification scheme requiring 4 of 11 criteria for research definition, although this is recognized to miss early and mild cases. Even so, there is under diagnosis because the presenting symptoms and signs are often not specific; and over diagnosis because doctors mistakenly use a positive blood test (present in 5% of the healthy population) by itself to make a diagnosis [1,2].

Accelerated atherosclerosis among these patients is a newly recognized phenomenon responsible for premature mortality. Treatment consists primarily of

immunosuppressive drugs (e.g., hydroxyl chloroquine [Plaquenil] and corticosteroids [prednisone]). In 2011 the FDA approved the first new drug for lupus in more than 50 years—belimumab [BENLYSTA®]. Morbidity and mortality may be related to late diagnosis, problems in access to care, less effective treatments, and poor compliance with therapeutic regimens [1,2].

2. Prevalence

Prevalence estimates vary widely, and range as high as 1,500,000 (Lupus Foundation of America) [3]. A recent study estimated a 2005 prevalence of 161,000 with definite SLE and 322,000 with definite or probable SLE [4]. In the USA, Congress has funded CDC to conduct two population-based SLE registries with the primary purpose of generating better prevalence (and incidence) estimates for Caucasians and African Americans. One is in Michigan (Washtenaw and Wayne Counties) and the other is in Georgia (DeKalb and Fulton Counties). New registries in California (San Francisco and San Mateo Counties) and New York City (Manhattan) are funded to generate similar estimates for Hispanics and Asians. The Indian Health Service is developing similar estimates for American Indians/Alaska Natives [3,4].

The reported prevalence of systemic lupus erythematosus (SLE) in the population is 20 to 150 cases per 100,000 [5,6,7]. In women, prevalence rates vary from 164 (white) to 406 (African American) per 100,000 [6]. Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century [8]. Estimated incidence rates are 1 to 25 per 100,000 in North America, South America, Europe and Asia [7,9,10,11]. Geographic and racial distribution — both geography and

race affect the prevalence of SLE and of frequency and severity of clinical and laboratory manifestations. The disease appears to be more common in urban than rural areas [6,12]. The prevalence of SLE is higher among Asians, Afro-Americans, Afro-Caribbeans, and Hispanic Americans compared with Americans of European descent in the United States, and among Asian Indians compared with Caucasians in Great Britain [10,13,14].

In comparison, SLE occurs infrequently in Blacks in Africa [15]. In New Zealand, the prevalence and mortality of SLE are higher in Polynesians than in Caucasians [16]. Photosensitivity and discoid skin lesions may be more frequent clinical manifestations in patients with Northern European than those with Southern European ancestry; the former group is, however, less likely to have anti-cardiolipin and anti-dsDNA antibodies [17].

Gender — the increased frequency of SLE among women has been attributed in part to an estrogen hormonal effect (see 'Hormonal factors' below) [18,19]. An estrogen effect is suggested by a number of observations including the female-to-male ratio of SLE in different age groups: in children, in whom sex hormonal effects are presumably minimal, the female-to-male ratio is 3:1 [20]. In adults, especially in women of child-bearing years, the ratio ranges from 7:1 to 15:1 [6,20]. In "older" individuals, especially post-menopausal women, the ratio is approximately 8:1 [20].

2.1. Incidence

In several places, national incidence data are difficult to obtain because onset is difficult to determine (non-specific symptoms and signs) and the required, resource-intensive studies are done in small areas. [21]. Existing estimates range widely, from 1.8 to 7.6 cases per 100,000 persons per year in parts of the continental United States [21]. Incidence rates in whites in Rochester, Minnesota (Mayo Clinic's Rochester Epidemiology Project) tripled from 1.5/100,000 in the 1950–1979 cohorts to 5.6/100,000 in 1980–1992 cohorts [22].

2.2. Mortality

From 1979 to 1998, the annual number of deaths with lupus as the underlying cause increased from 879 to 1,406. Crude death rates increased with age (35% were in 15–44 year age group), among women (5 times higher than in men), and among blacks (3 times higher than in whites). Death rates were highest and increased the most over time among black women aged 45–64 years [23]. An equivalent number listed lupus as a contributing cause of death. Causes of death are mainly active disease, organ failure (e.g., kidneys), infection, or cardiovascular disease from accelerated atherosclerosis. Among rheumatic conditions, lupus has a relatively high mortality (14.5% of all rheumatic disease mortality in 1997). At the same time, survival has been improving, suggesting that more or milder cases are being recognized [23].

3. Stress and SLE

It has been proved that stress worsens clinical signs and symptoms of patients with lupus. It is recommended to lupus patients to reduce the stress. It is based on numerous

studies where associations between daily stress and disease exacerbations have been demonstrated [24,25]. It is believed that the higher SLE prevalence seen in Afro-Americans is related to stress factors. They are poverty, high rates of unemployment, incarceration, violent crime, and homicide. They constitute a socio-biological disadvantage that can be accumulated at multiple points during the life of this population [26]. Stress-management programmes in a group of Afro-Americans demonstrated that workshop interventions can be effective in improving clinical signs and symptoms of SLE [25].

3.1. Perinatal Risk Factors for SLE

In a SLE study carried out in Sweden were identified 774 cases and 3337 controls; the age at which SLE was first observed ranged from 0 to 36 years old [27]. The high birth weight was not a risk factor for SLE as previously described, where birth weight > or =10 pounds was positively associated with SLE among women [27,28]. Males had a 2.4-fold increased odds of SLE if born preterm (<37 weeks; OR = 2.41; 95% CI 1.09, 5.36). Birth order was significantly associated with SLE, particularly among females. The odds of SLE were increased by 12% for every additional birth [27]. Being or not breastfed was not associated with SLE [28].

3.2. Cardiovascular Risk and SLE

The leading cause of mortality in the SLE patient population is cardiovascular disease at an age when women often have low cardiovascular risk. Hypertension is a major cardiovascular disease risk factor, and its incidence and prevalence are markedly increased in women with SLE [29].

3.3. The Use of Oral Contraceptives and SLE

The role of estrogens in SLE development is supported by studies from experimental SLE animal models in which early suppression of estrogens leads to attenuation of SLE disease parameters, including renal injury and autoantibody production [29]. However, in human SLE data about the role of estrogens are inconclusive and much less clear. Rojas-Villarraga et al, 2014 reported that hormonal replacement therapy (HRT) was associated with SLE development. No association was found when analyzing the risk for SLE among oral contraceptive (OC) users [30]. Others studies have reported conflicting results on this matter. There was a group of female affected with SLE in which the use of HRT or OC did not cause SLE exacerbation but in small amounts of SLE patients [31–32]. The fact that the female/male ratio in SLE can be as high as 15:1, suggests that environmental factors and hormones play an important role in the SLE immunopathogenesis.

3.4. Environmental Factors and SLE

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which both genetic and environmental factors are involved. Vitamin D is one such environmental factor that plays a specific function in the immune system, acting through a nuclear receptor (VDR) expressed in all immune cells. Several polymorphisms of the gene that encodes this receptor have been described. Carvalho et al, 2015 reported about a possible role of

VDR gene polymorphisms in SLE. Between VDR polymorphisms and SLE severity (chronic damage) a positive association was found. The occurrence of CT genotype of FokI seems to confer a worse prognosis in SLE [33]. The SLE etiology is still not fully understood. There is lack of concordance of the disease amongst genetically identical twins suggesting that both genetic and environmental triggers are likely to orchestrate the onset and flares of SLE [34,35].

A list of environmental factors, such as alcohol, ultraviolet light, cigarette smoke, chemicals, infections caused by Epstein Barr virus and parvovirus, hormones, and vaccines, have been linked to SLE development in many populations in case-control studies and several randomized controlled clinical trials [34,35,36,37]. Another environmental factor involved in the SLE immunogenesis is the drugs hydralazine, which is implicated in inhibiting T-cell DNA methylation; diet, and agents causing oxidative stress are also involved in the SLE genesis [38].

3.5. Genetic Factor and SLE

Several studies have been performed with TNF- α -308 G/A (rs1800629) single nuclear polymorphism (SNP) to evaluate the risk of SLE in various ethnicities. A genetic Polish study indicated that the TNF- α -308 G/A polymorphism may be a DRB1*03:01 haplotype, a dependent genetic risk factor for SLE; and concluded that this SNP was independently associated with renal manifestations and production of anti-Ro antibodies [39]. Another genetic study was carried out in European descendent patients and revealed that polymorphisms in STK17A gene are associated with systemic lupus erythematosus and its clinical manifestations, for example the haplotype TAGTC was associated to haematological alterations [40].

3.6. Immunological Factors and SLE

Excessive activity of dendritic cells (DCs) is postulated as a central disease mechanism in Systemic Lupus Erythematosus [41], this can be exacerbated by pro-inflammatory factors, in particular Type I IFNs, which modulate B cell function in lupus causing an alteration of the immunological tolerance [42]. In SLE autoantibodies form immune-complexes that are deposited in several organs and trigger inflammatory reactions followed by tissue damage. These auto-antibodies are mainly directed to nuclear antigens including DNA, histones, nucleoproteins, RNA among others [43].

3.7. Novel Therapeutic Options in SLE

A study was carried out to investigate whether an increase in vitamin D levels in SLE patients was associated with improvement in disease activity. To estimate the association between levels of 25(OH) D and various measures of disease activity longitudinal regression models were used. It was found that a 20-ng/ml increase in the 25(OH)D level was associated with a 21% decrease in the odds of having a high disease activity score and a 15% decrease in the odds of having clinically important proteinuria [41,44]. Another avenue for

immunotherapy is the generation of stable tolerogenic DCs that are able to induce and maintain regulatory T cell homeostasis in vivo [45]. T cell tolerance can be achieved by tolerogenic DCs, which have the capacity of blocking undesired autoimmune responses. Several molecules are expressed on DCs including TLRs, CD86, PDL-1 and Fc γ Rs which play a role in the innate and specific acquired immune responses [46].

A new monoclonal antibody promises to be an effective immunotherapy in SLE patients; its name is Epratuzumab, a humanized monoclonal antibody, which targets CD22 on B cells. It acts as B cell modulators, inhibiting signalling pathways of the B cell receptor. It has been shown to be efficacious in open-label and Phase I and Phase II randomized controlled trials [47,48]. In addition many purified intravenous immunoglobulins (IVIg) have been produced and they have been effective in the treatment of patients with SLE [49,50,51,52]. IVIg has been used due to its anti-inflammatory properties in recognized autoimmune disorders that include idiopathic thrombocytopenic purpura (ITP), Kawasaki disease, Guillain-Barré syndrome and other autoimmune neuropathies, myasthenia gravis, dermatomyositis and several rare inflammatory diseases [53].

There is not a consensus in the pharmacological effects of this therapy. We has published three cases of SLE which were consequently treated with a commercial IVIg named Intacglobin and all three cases were free of flares during the period of the treatment that was 1 year. We hypothesize that the immune-suppressing activity of IVIg may be due to its capacity to inhibit the production of autoantibodies, probably by blocking immunoglobulin receptors on B cells. The IVIg therapy contains opsonins, which may improve the phagocytosis of immunocomplexes by antigen-presenting cells [49,54]. In addition, IVIg can be given to patients with hypogammaglobulinemia-associated SLE [55] and also to patients with infections due to its polyclonal antibody overload against many microorganisms. IVIg causes neutralization and IgG-complement mediated lysis [56].

Some of the treatment strategies have focused on blocking IFN α or its receptor and others the plasmacytoid dendritic cell (pDC), which is the principal IFN α producing cell [57]. Rituximab is a monoclonal antibody, which specifically depletes B lymphocytes and it has been used successfully in the management of steroid-resistant autoimmune thrombocytopenia [58] and childhood-onset SLE [59]. When rituximab is administrated at an earlier stage, it prevents irreversible vital organ damage [60].

4. Conclusion

When we look at SLE we are seen the iceberg's pick, so it is very important to have in mind the several triggers that can cause this disease for a prompt diagnosis specially when it occurs in ethnic groups with low SLE prevalence. Fortunately today we have a number of therapies that are available to treat this rheumatic disorder, for example IVIg and Rituximab together with much traditional treatment including steroids. However, SLE hides behind other rheumatic or inflammatory disorders and constitutes a professional challenge to us. Several new drugs for SLE have shown to be efficacious in open-label and Phase I

and Phase II randomized controlled trials, which represented advancement in medical sciences.

Competing Interests

The authors declare that no competing interests exist.

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