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Original article

Systemic Lupus Erythematosus: An Overview of Pathogenesis, Prevalence, Diagnosis, Classification Criteria, Management, Challenges, and Future Directions

Balid Albarbar[1]*, Hanan Aga[2], Sabri Shalbi[3]

[1]*Department of Medical Laboratory, Higher Institute of Sciences & Medical Technology, Alkums, Libya*
[2]*Department of Nursing, Higher Institute of Sciences & Medical Technology, Alkums, Libya*
[3]*Department of Diagnostic and Therapeutic Radiology, Higher Institute of Sciences & Medical Technology, Alkums, Libya*
***Corresponding Email**: B.albarbar@yahoo.co.uk*

ABSTRACT

Systemic Lupus Erythematosus (SLE) is a complex, chronic autoimmune disease characterized by widespread inflammation and tissue damage across multiple organ systems. This paper aims to review the SLE pathogenesis, prevalence, diagnosis, classification criteria, management, challenges, and future directions. Scientific literature pertaining to SLE was analyzed through comprehensive searches in specialized academic resources, including PubMed and Google Scholar. This review explores the multifaceted nature of SLE, pathogenesis, which involves a complex interplay of genetic, environmental, and immunological factors leading to the loss of self-tolerance and autoantibody production. The epidemiology section highlights the varying incidence and prevalence of SLE globally. We review current diagnostic approaches, including clinical evaluation and laboratory tests, which are crucial for early and accurate diagnosis. The classification criteria, as outlined by established guidelines, are discussed to provide insight into the diagnostic framework used to identify and categorize SLE. SLE management is briefly addressed, including issues related to disease heterogeneity. Finally, we explore future directions in SLE research, focusing on emerging therapies. Despite advancements, the management of SLE remains challenging, necessitating ongoing research efforts to improve diagnostic precision, therapeutic efficacy, and patient outcomes.

Keywords: Autoimmune Disease, Immune System, Antibodies, Systemic Lupus Erythematous.

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الذئبة الحمامية الجهازية هي مرض مناعي ذاتي مزمن معقد يتميز بالتهاب واسع النطاق وتلف الأنسجة عبر أنظمة أعضاء متعددة. تهدف هذه الورقة إلى مراجعة مسببات مرض الذئبة الحمامية الجهازية وانتشاره وتشخيصه ومعايير التصنيف والإدارة والتحديات والاتجاهات المستقبلية. تم تحليل الأدبيات العلمية المتعلقة بمرض الذئبة الحمامية الجهازية من خلال عمليات بحث شاملة في الموارد الأكاديمية المتخصصة، بما في ذلك PubMed وGoogle Scholar. يستكشف هذا الاستعراض الطبيعة المتعددة الأوجه لمرض الذئبة الحمامية الجهازية، والمسببات المرضية، والتي تنطوي على تفاعل معقد بين العوامل الوراثية والبيئية والمناعية التي تؤدي إلى فقدان تحمل الذات وإنتاج الأجسام المضادة الذاتية. يسلط قسم علم الأوبئة الضوء على التفاوت في حدوث وانتشار مرض الذئبة الحمامية الجهازية على مستوى العالم. نستعرض مناهج التشخيص الحالية، بما في ذلك التقييم السريري والاختبارات المعملية، والتي تعد حاسمة للتشخيص المبكر والدقيق. تتم مناقشة معايير التصنيف، كما هو موضح في المبادئ التوجيهية المعمول بها، لتوفير نظرة ثاقبة للإطار التشخيصي المستخدم لتحديد وتصنيف مرض الذئبة الحمامية الجهازية. يتم تناول إدارة مرض الذئبة الحمامية الجهازية بإيجاز، بما في ذلك القضايا المتعلقة بتباين المرض. أخيرًا، نستكشف الاتجاهات المستقبلية في أبحاث الذئبة الحمامية الجهازية، مع التركيز على العلاجات الناشئة. وعلى الرغم من التقدم، لا تزال إدارة الذئبة الحمامية الجهازية تشكل تحديًا، مما يستلزم بذل جهود بحثية مستمرة لتحسين دقة التشخيص وفعالية العلاج ونتائج المرضى.

INTRODUCTION

Autoimmune diseases are various group of disorders result from the immune system failure to distinguish between self and non-self-antigens, leading to immune-mediated damage to healthy tissues. This dysregulated immune response can disturb any organ or system in the body reviewed recently in references [1–3]. The most common autoimmune diseases include: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and type-1 diabetes mellitus (T1DM), as well as organ-specific autoimmune diseases like Hashimoto's thyroiditis and multiple sclerosis (MS) [1,2,4]. SLE is a chronic autoimmune disease characterized by dysregulation of the immune system, resulting in inflammation and tissue damage in multiple organs and tissues of the body [5]. Advances in diagnostic techniques, including the identification of novel biomarkers and imaging modalities, offer promise for earlier and more accurate diagnosis for suspected cases. In addition to that emerging therapies targeting specific pathways involved in SLE pathogenesis are being investigated, aiming to improve disease management and outcomes reviewed in references [6–9]. This paper aims to review SLE disease, including pathogenesis, epidemiology, classification criteria, diagnosis, and SLE management.

Pathogenesis

Recent insights into the pathogenesis of SLE continue to deepen our understanding of this complex autoimmune disease. While the exact cause of SLE remains elusive, research has identified several key factors contributing to its development and progression. The etiology of SLE is multifactorial, involving a complex interplay of genetic, environmental, hormonal, and immunological factors. While the exact cause remains incompletely understood, five key components may contribute to the development of SLE [10]. Genetic factors play a significant role in SLE susceptibility. Studies indicated several genetic variants that associated with risk of developing SLE. These genetic factors (these include genes related to the HLA region, cytokines, and interferon pathways) influence immune system regulation response to environmental triggers, and the production of autoantibodies targeting self-antigens [11–13]. On the other hand, various environmental factors can trigger or exacerbate SLE in genetically susceptible individuals. Common triggers for SLE disease include ultraviolet (UV) light exposure, certain medications (e.g., hydralazine, procainamide), or infections (e.g., Epstein-Barr virus - EBV), and hormonal changes (e.g., estrogen fluctuations) [14–16]. Also, hormonal factors, particularly estrogen, may contribute to the pathogenesis of SLE. Estrogen has immunomodulatory effects and can enhance B-cell activation, promote autoantibody production, and modulate T-cell function. Fluctuations in estrogen levels during puberty, pregnancy, and hormonal contraceptive use have been associated with SLE flares [17–20]. Dysregulated immune responses, including aberrant activation of B cells, T cells, and dendritic cells, as well as impaired clearance of apoptotic cells [15,21–24]. Epigenetic changes include DNA methylation, histone modifications, and microRNA dysregulation, contribute to the unusual gene expression in SLE [25]. These triggers may induce immune dysregulation, promote autoantibodies production, and contribute to tissue inflammation and damage [14].

Dysfunction in B cells, T cells subsets (particularly T regulatory cells and Th17), and dendritic cells [26], contribute to the inflammatory milieu in SLE [17,22,27–29]. A study reported the role of Neutrophil Extracellular Traps (NETosis) in SLE, NETosis, a process where neutrophils release DNA and proteins to form extracellular traps, has been implicated in SLE pathogenesis. Abnormal NET formation can trigger autoantibodies production and contribute to tissue damage in SLE [30]. Moreover, dysregulation of cytokine signaling pathways, particularly type I interferons (IFNs) and pro-inflammatory cytokines such as, interleukin-6 (IL-6) [31], and tumor necrosis factor-alpha (TNF-α) play critical role in SLE

pathogenesis [32,33]. Studies have highlighted the dysregulation of IFN signaling pathways and the presence of IFN gene signatures in SLE patients, underscoring their potential as therapeutic targets [21].

Abnormal cytokine production contributes to immune activation, tissue damage, and the amplification of inflammatory responses [21]. Overall, understanding the multifaceted pathogenesis of SLE is crucial for developing targeted therapeutic strategies aimed at modulating immune dysregulation, reducing inflammation, and improving outcomes for individuals living with this chronic autoimmune disease.

Epidemiology

The epidemiology of SLE involves understanding the prevalence, incidence, demographic patterns, and associated risk factors of the disease across different populations [4]. SLE incidence varies significantly across different regions and populations. However, it's generally more prevalent in certain ethnic groups, particularly individuals of African, Asian, and Hispanic descent, compared to those of European descent [34,35]. North America, particularly the United States, has one of the highest reported incidence rates of SLE. Within the United States, there are also variations in incidence rates among different racial and ethnic groups, with higher rates observed among African American, Hispanic, and Native American populations compared to Caucasians [36–38]. In Europe, SLE incidence rates tend to be lower compared to North America, but there are still variations among different ethnic groups within Europe. In Asia, SLE incidence rates vary widely across different ethnic groups. For example, studies have reported higher incidence rates in certain populations in China and Japan compared to others. Similarly, in Africa and Latin America, SLE incidence rates vary among different regions and ethnic groups [36–38].

SLE tends to be more prevalent in regions closer to the equator, suggesting a potential role of environmental factors such as sunlight exposure and vitamin D levels in the development of the disease. SLE predominantly affects women, with a female to male ratio ranging from 9:1 to 15:1 at any age typically between ages 15 to 45 years, see recent studies in references [35,39,40]. Taken together, the epidemiology of SLE highlights its complex nature, influenced by genetic, environmental, and demographic factors. Understanding these aspects is crucial for effective management, prevention strategies, and advancing research efforts aimed at improving outcomes for individuals who affected by SLE disease.

Diagnosis

SLE diagnosis relies on symptoms, laboratory tests, and imaging tests. Diagnosis begins with a thorough clinical assessment for the patient, including a detailed medical history and physical examination [7,41,42].

Classification criteria

Classification criteria, such as the Systemic Lupus International Collaborating Clinics (SLICC) criteria or the American College of Rheumatology (ACR) criteria, are organizations for the diagnosis of SLE disease. The most widely used classification criteria for SLE are the ACR classification criteria, also known as the "Eleven criteria" as shown in table 1, which were updated in 2019 [43,44].

Table 1. Classification criteria for SLE disease

Criteria	Description
Malar rash	Butterfly-shaped rash over the cheeks
Discoid rash	Red, scaly patches that may scar
Photosensitivity	Skin rash in reaction to sunlight
Oral ulcers	Include sores in the mouth or nose
Nonerosive arthritis	Inflammation in two or more peripheral joints
Pleuritis or pericarditis	Inflammation of the lining around the lungs or heart
Kidney disorder	Persistent protein or cellular casts in urine

Neurologic disorder	Seizures or psychosis without known cause
Hematologic disorder	Anemia, low white blood cell count, or low platelet count
Immunologic disorder	Positive results for anti-dsDNA or anti-Smith
Antinuclear antibody	Positive results for ANA in blood

A patient is classified as having SLE disease if he/she meets at least 4 of these 11 criteria, including at least one clinical criterion and one immunologic criterion. These criteria are designed to distinguish SLE from other autoimmune or rheumatic diseases [43,44].

Laboratory tests

First, anti-nuclear antibodies (ANA) testing is typically the first screening test for SLE. While ANA positivity is not specific to SLE and can be found in other conditions of autoimmune disease, a high level of ANA is often seen in patients with SLE [8,45]. Second, antibody double-stranded DNA (Anti-dsDNA) are also highly specific for SLE and are associated with active disease and renal involvement [8]. Third, anti-Smith (Anti-Sm) are highly specific biomarker for SLE [8].

Reduced levels of complement proteins, particularly complement; C3 and C4, are commonly seen in active SLE due to complement consumption [7,46]. Additional laboratory tests are also include complete blood count (CBC) to detect anemia and leukopenia and also urinalysis may be useful to detect proteinuria or cellular casts [47]. Also, circulating micro RNA (miRNAs) have emerged as potential biomarkers for diagnosing disease activity in SLE [48].

Imaging tests

X-rays may be used to assess joint damage or organ involvement such as chest X-ray for pleuritis. Other imaging studies such as renal ultrasound or biopsy for evaluating lupus nephritis, and chest X-ray or computed tomography (CT) scan for assessing pulmonary involvement, may be performed based on clinical indications [7].

Differential diagnosis

Previous studies reported that SLE can mimic other autoimmune diseases and infections [7,17]. Differential diagnosis may include, rheumatoid arthritis, sjögren's syndrome, dermatomyositis and viral infections. Diagnosis of SLE is often require specialists involving rheumatologists, dermatologists, nephrologists and other, depending on the organ systems involved. Accurate and timely diagnosis of SLE is essential for initiating appropriate treatment and preventing disease-related complications [7,17].

Management

Prevention of SLE is challenging due to its complex multifactorial etiology involving genetic, environmental, and hormonal factors. However, certain strategies may help reduce the risk of developing SLE or prevent flares in individuals already diagnosed with the condition [7,17,49]. Treatment of SLE typically involves medications aimed at controlling inflammation, suppressing the immune system, and managing symptoms. Common medications used are including biologic therapies, antimalarial drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressants [22,41,42,50]. Taken together, effective management of SLE requires a multidisciplinary approach, individualized treatment plans, and ongoing collaboration between healthcare providers and patients to optimize outcomes and improve quality of life.

Challenges and future directions

SLE manifests with diverse clinical presentations (heterogeneity of disease) and disease courses, complicating diagnosis and treatment. In addition to that, there is a growing emphasis on identifying biomarkers and developing personalized treatment strategies based on individual genetic, immunologic, and environmental profiles. However, progress has been made with targeted biologic therapies (e.g., anti-B cell therapies, interferon inhibitors), challenges remain in achieving sustained remission and

managing treatment-related risks. Continued research efforts aimed at unraveling the complexities of SLE pathogenesis, refining diagnostic methods, and developing targeted therapies hold promise for improving lives for individuals living with this chronic autoimmune disease particularly SLE disease.

CONCLUSION

SLE is a type of autoimmune disease characterized by dysregulated immune responses, inflammation, and tissue damage affecting function of multiple organs. Recent advancements in our understanding of SLE disease, pathogenesis, diagnosis, and management have provided insights into the genetic, environmental, hormonal, and immunological factors contributing to the disease. Effective management requires a multidisciplinary approach, personalized treatment plans, and ongoing collaboration between healthcare providers and patients.

Conflict of interest. Nil

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