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Haematological Pattern of Early Diagnosis of Systemic Lupus Erythematosus; Experience from Low Resource Economy

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A B S T R A C T

Background: Systemic lupus erythematous is a chronic autoimmune disorder that impacts multiple organ systems, with an estimated incidence of 0.5 per 100,000 people. The prevalence and treatment of this condition are, however, different in low-income countries than in high-income countries. In low resource economies, the disease, however, is more deadly and generally more severe. Although the exact cause of the etiology in low resource economies is unknown, it is believed to be a result of a combination of genetic, environmental, and hormonal factors, with a possible contribution from infections agents and limited access to healthcare. The apparently low incidence of previously reported SLE may be attributed to low disease detection, particularly in primary health care, limited access to testing facilities, underdiagnosis due to limited access to health services, and shortage of specialists. However, second or third-line medications are not commonly used because patient pay out-of-pocket, high cost of drugs, and inadequate NHIS coverage.

Objective: To review the processes for diagnosis of SLE in low resource economy as well as current treatment options in use for the disease. To outline the challenges resulting from the unavailability of diagnostic equipment, especially in poor resource areas.

Methodology: This is a systematic review conducted over 10 years (January 2013 to December 2022) in order to find pertinent information on the diagnosis and available treatments for the disorder in our environment, it was designed to randomly access research publications using search engines, with reference to valid studies from academic sources like Research Gate, PubMed and Google Scholar. We also evaluated various related titles, abstracts and full reports for eligibility.

Results and conclusion: Anemia, Leucopenia, Lymphopania, Neutropenia, Thrombocytopenia and Elevated ESR are the major clinical features seen in patients with SLE and can be used for early diagnosis. Treatment options for SLE in our environment are often limited to steroids, Hydroxychloroquine and Nonsteroidal anti-inflammatory drugs. Biologic agents and immunosuppressant's are less used and often not available. There is a need for larger future studies and increasing the NHIS coverage into making more affordable and accessible diagnostic and treatment options.

Introduction

Connective tissue inflammations are symptoms of the chronic autoimmune condition Systemic Lupus Erythematosus (SLE) [1]. Multisystemic microvascular inflammation and the production of many autoantibodies, in particular antinuclear antibodies (ANA), are its defining characteristics. Every organ and tissue in the body is typically susceptible to SLE, and each patient will experience the disease in a unique way with regard to how it manifests clinically [2]. The complex interplay between genetic predisposition, environmental risk factors and hormonal status results in clinical heterogeneity in the clinical presentation of systemic lupus erythematosus, making its often difficult diagnosis highly dependent on clinical experience and immunological findings [3-5]. Almost every organ system may be affected by this potentially fatal autoimmune condition.

Depending on demographic, socioeconomic factors, and specific ethnic population groups, the total incidence of SLE ranges from 1.6 to 21.9 cases per year. 100,000 populations per year, with prevalence ranging from 7.4 to 159.4 cases [6]. Childhood is where up to 20% of cases start. Pediatric SLE patients are more likely than adult SLE patients to have neurologic and renal involvement as well as to develop more renal damage [7]. Both renal and neurological involvement are regarded as severe disease manifestations. In the course of their illness, 20 to 60 percent of SLE patients develop renal involvement

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[8], with young black women [9–10] having the highest risk of renal disease and renal failure. Because the disease has so many guises, diagnosing SLE can be challenging. A manifestation of the disease called lupus nephritis (LN) also exhibits these many faces [10].

In particular, lupus nephritis (LN) is associated with significant morbidity and poor survival in patients who progress to end-stage renal disease (ESRD) and require renal replacement therapy. Due to potential medical conditions that may develop during the course of the disease, people with lupus frequently have special nutritional needs. These ailments include kidney disease, diabetes, or osteoporosis brought on by the use of steroids [9]. SLE pathogenesis, diagnosis, and care are all closely related.

According to physician Rogerius' description of the first known case of lupus, it occurred in the 13th century [11]. The majority of clinical descriptions of lupus between the Middle Ages and the Mid to Late Nineteenth Century were dermatological, according to Bateman, Cazenave, and Kaposi [11]. Finally, research by Hughes and others helped us to understand the antiphospholipid antibody syndrome as a crucial component of lupus [12]. The distribution of SLE has not yet been the subject of a systematic review that has been published. [11,21,29]. This review is aimed at providing a broad insight into SLE prevalence and incidence in low resource economy on a global and regional scale.

MATERIALS AND METHODS

Study design: This is a systematic review that describes the processes for diagnosis of SLE in low resource economies as well as current treatment options in use for the disease. This study was designed to randomly access research publications to check for relevant information on diagnosis and treatment options of the diseases in low-income countries in the last 10 years. PubMed, Google Scholar, Science Direct and Elsevier were used to search for published studies in English. The following keywords were used in the search strategy: (Diagnosis AND Systemic Lupus Erythematosus) AND (Management AND SLE) AND (low resource economy OR developing countries) AND (SUSPICIOUS) AND Humans AND English. The objective was to identify studies that details the diagnosis and management of SLE in developing countries/ low resource economies to better examine how physicians evaluate the severity of presenting symptoms of the disease. Inclusion criteria for this study is that the study identifies the incidence, prevalence, epidemiology, and treatment/management patterns in developing countries. Furthermore, specific studies on the perspective of physicians on SLE in Nigeria were selected as these studies provided a critical appraisal opportunity for comparing SLE practices in Nigeria as against other countries. Studies were excluded if the study did not present longitudinal data (either retrospective or prospective) for the development of SLE or refers to treatment patterns in developed nations. A three-step process was used to evaluate publications for inclusion.

i. The lead investigator evaluated the titles and summaries of all identified studies.

ii. Then, independent inclusion criteria were applied to the full texts of pertinent articles.

iii. Author(s) extracted the data.

Selection of the study:

Research papers that met the inclusion criteria were accepted based on the title and abstract, while those that didn't were excluded.

RESULTS AND DISCUSSION

Epidemiology of SLE

Worldwide, both sexes, all racial/ethnic groups, and all age groups are affected by the disease known as systemic lupus erythematosus (SLE). Nevertheless, larger prevalence is seen in, women, adults and non-Caucasians. These variations as well as the disease's variable course and outcome are caused by genetic, environmental, sociodemographic, and methodological factors. Non-Caucasians are more likely to develop a severe disease with early mortality and damage accumulation risks. Although studies have not conclusively shown that being a man makes lupus worse, men do have a more severe disease. Lastly, lupus that develops later in life is majorly insignificant but is linked to higher damage accrual and reduced survival. Childhood-onset lupus is linked to a more severe disease, as well as higher damage and diminished survival. Demographics, socioeconomic factors, and certain racial populations, such as Hispanics, blacks, and Asians all have a significant impact on the incidence and prevalence of SLE [13-15]. African Americans [16,17], American Indians, and Alaska Natives [18,19] in particular have higher predilection and worse outcomes from SLE than Caucasians in the same contexts in Europe and North America [20]. Aboriginal/ indigenous people have a two- to four-fold higher prevalence of SLE disease than non-aboriginal people in Australia, Canada, and the United States of America [21]. In addition, patients of Asian and African descent were more likely than whites to have more clinical manifestations, active episodes of SLE, and higher mortality [22]. According to some reports, SLE is common in Africa [16,17], but this claim may have been influenced by the clinical minutiae and difficulty of diagnosing the condition. However, according to recent reports, sub-Saharan Africa had a lower prevalence of SLE than Asia-Pacific nations at 17% (0.8-29%) [23]. Overall prevalence for SLE in Asian nations were 0 t-3 and 4-45 per 100,000, respectively [24]. Additionally, the prevalence of SLE in North America and Europe, respectively, ranged from 3.7 to 49 and 1.5 and 7.4 per 100,000 person-years [25]. Evidence also suggests that the prevalence of SLE is steadily rising in North America, Europe, and Asia [26]. However, study design reporting bias, case definitions, and SLE classification criteria may also contribute to population differences in SLE prevalence. [26]. Despite SLE's variability across all age groups, this age range is where it is most prevalent [27]. According to research, an increased risk of renal, neuropsychiatric, and cardiopulmonary disease accounts for 10–20 percent of patients with SLE disease beginning in childhood [28–30]. With a male to female patient ratio of 1:9, the gender disparity of SLE is also widely acknowledged. At 15–44 and 45–64 years of age, respectively, are typically when SLE in females occurs and is most prevalent [31]. The prevalence and incidence of SLE vary across the different parts of the world due to environmental, genetic, and racial factors. Changes in environmental factors, for example, are linked to an increase in SLE [32]. In addition, factors such as education level, health insurance status, income level, race, medication adherence, and social support may influence the severity and course of SLE. Survival of SLE patients in LMICs is lower than in high-income countries due to higher mortality, inadequate interventions, and infectious comorbidities [33].

Results of a recent study by Fatoye *et al.* 2022 demonstrated that SLE is prevalent in LREs and that there is a significant amount of variation across these nations. This variation can be attributed to a number of things, such as the definition of SLE used, ethnic and geographic differences in the populations being studied, access to healthcare, environmental factors (infections and ultraviolet light), and case identification techniques. The prevalence and incidence estimates of SLE show that women are more likely than men to have the disease, despite the ratio fluctuating with a current ratio close to 9:1. This might be because oestrogen, which stimulates lymphocytes, continues to be more active in women [34]. Additionally, there are observable differences in immunity between men and women, which may also affect how each responds to the risk of SLE [35,36]. The prevalence and incidence rates of SLE ranged from 3 to 3 per 100,000 people and 1 to 8 per 100,000 individuals, respectively. In Colombia and Ukraine, respectively, SLE prevalence rates were found to be the highest and lowest.

SLE has been described all over the world, but the African continent seems to be the exception rather than the rule. However, Afro-Caribbean, African-American, and Afro-Latin-Americans of

African descent are surprisingly more likely to develop SLE than other populations. The "prevalence gradient" hypothesis, which states that people of African descent have different genetic makeup and environmental exposures than their countries of origin that predispose them to a higher incidence of SLE, offers an explanation. In addition, reduced survival affects prevalence. It should be noted that no reliable distribution data are available for West Africa; instead, conclusions are usually drawn from studies of immigrant women in the United Kingdom, which found that they had a three-fold higher prevalence of SLE than Caucasian patients but a lower prevalence than Afro-Caribbean patients [38].

Mortality and Survival of SLE patients in Low Resource Economy

Over the past 60 years, there has Been an improvement in the survival of SLE patients around the world, with the five-year survival rate rising from about 50% in the 1950s to about 95% in the 2000s [39]. This apparent improvement may be due to earlier diagnosis and better management of the disease and its sequelae. Of note, the standardized mortality rate (SMR) of SLE is 2.6–3.0 times higher than that of the general population. This is likely due to higher rates of infections (SMR = 5.0), kidney disease (SMR = 4.7), and cardiovascular disease (SMR = 2.3) [40]. Although a breakdown for causes related to the heart, the kidneys, and infections is not available [41], the SMR is even higher in children with SLE. Since the middle of the 1970s, a bimodal pattern of mortality has been observed in SLE patients, with those who die early in the course of the disease dying from infections or active disease. Those who died later died of cardiovascular disease and generally had inactive disease at the time of death [42]. As noted above, many variables, including age at diagnosis, gender, race, and socioeconomic status factors, were associated with higher mortality.

AETIOLOGY

Systemic lupus erythematosus (SLE) is still difficult to diagnose and has an unknown etiology. A variety of genetic and environmental factors typically interact. Disease susceptibility is influenced by numerous genes. This susceptibility and the clinical manifestation of the disease are modified by the interaction of sex, the hormonal environment, and the hypothalamo-pituitary-adrenal axis. Defective immune regulatory mechanisms, such as the removal of apoptotic cells and immune complexes, are significant causes of SLE. B cell hyperactivity and the production of pathogenic autoantibodies are caused by immune tolerance loss, an increased antigenic load, excessive T cell assistance, improper B cell suppression, and a switch from T helper 1 (Th1) to T helper 2 (Th2) immune responses. Last but not least, it's likely that specific environmental factors are needed to start the disease. The cause of the immune system disorder underlying SLE is currently unknown. Clinical manifestations of disease are undoubtedly the result of multiple environmental and immune triggers acting on genetically susceptible individuals. Abnormalities of T cells, B cells, dendritic cells, Fc receptors, proinflammatory cytokines, the complement pathway, and apoptosis have been identified and are believed to be involved in the pathogenesis of SLE.

PATHOSPHYSIOLOGY

As the process that results in the onset of disease, the pathophysiology of SLE is known. In the pathogenesis of SLE, the production of autoantibodies is the sentinel event. These autoantibodies may appear years before clinical signs of SLE [43]. The immune system eventually becomes further dysregulated as a result of immune complex formation, tissue deposition, and complement activation. Patients with lupus typically exhibit high IFN- activity [44]. The production of IgG and IgA antibodies may rise as a result of IFN-'s promotion of B-cell responses and immunoglobulin class switching [45]. Apoptosis, or "programmed cell death," appears to accelerate the progression of SLE. The disease is accompanied by impaired clearance of apoptotic bodies by the phagocyte/macrophage system, resulting in an increased apoptotic burden of circulating self-DNA or self-RNA complexes. They become antigenic targets of humoral and cell-mediated autoimmune responses. SLE can also be caused by epigenetic disturbances affecting DNA methylation, noncoding RNA histone modifications, and nucleosome remodeling [46]. The range of factors covered below serves as an example of how complicated the pathogenesis of SLE is.

Table 1 Genes involved in human systemic lupus erythematosus

HLA genes
DR2, DR3 (relative risk 2–5)
DR2, DR3, DR7, DQw1, DQw2, DQA1, DQB1, B8 (anti-Ro)
DR3, DR8, DRw12 (anti-La)
DR3, DQw2, DQA1, DQB1, B8 (anti-Ro and anti-La)
DR2, DR3, DR7, DQB1 (anti-DNA)
DR2, DR4, DQw5, DQw8, DQA1, DQB1 (anti-U1 ribonuclear protein)
DR2, DR4, DR7, DQw6, B61 (anti-Sm)
DR4, DR7, DQ6, DQ7, DQw7, DQw8, DQw9 (anticardiolipin or lupus anticoagulant)
Complement genes (C2, C4, C1q)
Non-HLA genes
Mannose binding lectin polymorphisms
Tumour necrosis factor α
T cell receptor
Interleukin 6
CR1
Immunoglobulin Gm and Km
FcγRIIA (IgG Fc receptor)
FcγRIIIA (IgG Fc receptor)
PARP (poly-ADP ribose polymerase)
Heat shock protein 70
Humhr 3005

HLA, human leucocyte antigen; Sm, Smith antigen.

Genetic Susceptibility

Susceptibility to disease is influenced by several genes. In a small number of patients, a single gene is responsible. For example, patients at risk for systemic lupus erythematosus or a lupus-like disease have homozygous defects in early complement components [47]. Most of the remaining patients require multiple genes. At least four susceptibility genes are thought to be required for the onset of the disease. The major histocompatibility complex (MHC) genes have been the most intensively studied of the three genetic components for their role in human systemic lupus erythematosus. Human leukocyte antigen (HLA) class II polymorphisms are associated with susceptibility to SLE in a population-based study. HLA DR2 and DR3 are frequently associated with SLE in patients of different ethnic origins, with a relative risk of developing the disease of 2 to 5 per 1000 [48]. The presence of specific autoantibodies, including those against the nuclear ribonuclear protein nRNP, the small nuclear ribonuclear protein sm, the ribonuclear protein ro, the ribonuclear protein la, and the DNA, has also been linked to the HLA class II genes [49]. Inherited complement deficiencies are another MHC gene system that affect disease susceptibility. In some ethnic groups, the HLA class III genes, especially those that encode the complement subunits C2 and C4, increase the risk of SLE. No matter their ethnicity, people who have homozygous C4A null alleles are at a high risk of developing SLE. Additionally, C1q, C1r/s, and C2.4 deficiencies are hereditary in SLE patients. Decreased complement activity can impair the neutralization and clearance of self and foreign antigens and thus increase susceptibility to disease. Autoimmunity may result when the immune system's ability to clear antigens is overpowered by their antigen burden.

Sex, Hormones and Hypothalamo-Pituitary-Adrenal Axis

SLE affects women more often than men [50]. It is uncommon for SLE to develop for the first time before puberty or after menopause [51]. Outside of the reproductive age range, the female preference becomes less obvious. In addition, SLE is more likely to develop in people with Klinefelter's syndrome, which is characterized by hypergonadotrophic hypogonadism [52]. These findings imply that endogenous sex hormones play a part in the development of disease. Both male and female SLE patients have been shown to have abnormal oestrogen metabolism, which results in significantly higher concentrations of 16-hydroxyestrone [53]. More potent and feminizing oestrogens are found in the 16-metabolites. Dehydroepiandrosterone (DHEA), testosterone, dihydrotestosterone, and dehydroepiandrosterone sulfate are among the androgens with low plasma levels in SLE-affected women [54,55]. Increased tissue aromatase activity or increased testosterone oxidation at C-17 may both be responsible for this anomaly. Androgen concentrations and disease activity are inversely correlated [56]. Low plasma testosterone levels and increased luteinizing hormone (LH) values [57] been discovered in some men

with SLE. In men and women with SLE, excessive oestrogenic but insufficient androgenic hormonal activity may therefore be to blame for the altered immune responses.

Auto-antibodies

Production of autoantibodies is the main immunological abnormality in SLE patients. In addition to soluble molecules like IgG and coagulation factors, these antibodies target a number of self-molecules that are present in the cytoplasm, nucleus, and cell surface. Over 95% of patients have antinuclear antibodies, which are the most typical and prevalent. Patients with SLE are the only ones with anti-ds-DNA and anti-Sm antibodies. In fact, the classification criteria for SLE include their presence [58]. The Sm antigen, known as small nuclear ribonucleoproteins (snRNPs), consists of a unique set of uridine-rich RNA molecules that bind to a common collection of nuclear proteins and other proteins associated with RNA molecules. Anti-DNA antibodies bind to conserved nucleic acid determinants that are ubiquitous on DNA, whereas anti-Sm antibodies react with snRNP core protein. Anti-Sm antibody titers are usually constant, whereas anti-DNA antibody titers often change with time and disease activity. Anti-ribosomal P antibodies and psychosis, anti-ribosomal Ro antibodies and congenital heart block and subacute cutaneous lupus are associated with autoantibodies and some clinical features of SLE; however, the pathogenicity of these antibodies has not been fully investigated. It is not clear exactly how the damage to the immune system occurs. The pathogenesis of manifestations other than glomerulonephritis is unknown, although deposition of immune complexes by complement activation at the relevant sites is a possible mechanism. This is shown by the regular co-occurrence of hypocomplementemia and vasculitis symptoms at the sites of active SLE. Other potential mechanisms include direct antibody-mediated injury and cell-mediated cytotoxicity on target tissues.

Disruptions of the Immune Reaction

SLE is characterized by a wide range of immune system abnormalities that affect B cells, T cells, and monocytic lineage cells, leading to polyclonal B cell activation, an increase in the number of antibody-producing cells, hypergammaglobulinemia, the production of autoantibodies, and the formation of immune complexes. The differentiation and activation of autoantibody-forming B cells appears to be assisted excessively and uncontrollably by T cells, and this appears to be the final common pathway. Specific antigens must stimulate B and T cell activation. Anti-DNA antibodies can be produced in mice by irritating chemicals like pristine, bacterial DNA and cell wall phospholipids, and viral antigens [59]. Autoantibodies can also be induced by autoantigens, such as DNA-protein and RNA-protein complexes [60]. Self and environmental antigens bind to induced antibodies on the surface of B cells or are taken up by professional antigen-presenting cells (APCs). Both professional APCs and B cells convert antigens into peptides and deliver them to T cells using HLA molecules on their surface. The B cells are then stimulated by the activated T cells to produce harmful autoantibodies. A second signal must be initiated by accessory molecules from the CD40/CD40L and B7/CD28/CTLA-4 systems in addition to contact stimulation, which is promoted by several cytokines, including IL-10.

Cytokine Network in SLE

Based on the recently discovered role of IL-10 in the pathogenesis of SLE, IL-2 production by lupus T cells in vitro may be impaired for several reasons, one of which is the downregulation of specific Th2 cytokines. A Th2 cytokine called IL-10 is a potential mediator of polyclonal B cell activation in SLE because it is a potent stimulator of B cell proliferation and differentiation. Indeed, recent studies have shown that spontaneous IL-10 production in peripheral blood B cells and monocytes is significantly higher in SLE patients than in controls [61,62]. Non-T cell populations in PBMCs from SLE patients expressed significantly more IL-10 transcripts compared to controls. Additionally, serum IL-10 levels are higher in SLE patients compared to controls and are associated with clinical and serological disease activity as well as anti-DNA antibody levels [63–65]. Furthermore, the activity of the disease is correlated with an elevated ratio of IL-10 to interferon-secreting cells in the PBMCs of SLE patients [66].

DEFECTIVE IMMUNE REGULATION

Patients with SLE have a defect in the way phagocytic cells clear immune complexes. This is due in part to the decreased number of CR1 complement receptors and functional issues with the cell surface receptors [67,68]. Inadequate phagocytosis of IgG2 and IgG3-containing complexes can also lead to defective clearance. The IgG receptors (FcR) exhibit allelic polymorphisms, which have recently been described. The Fc portions of IgG2 and IgG3 are less bound by some polymorphic alleles (FcRIIA and FcRIIIA), which results in impaired immune complex clearance [69]. Indeed, in some ethnic groups, the FcRIIA and FcRIIIA genotypes have been linked to nephritis and SLE susceptibility [70]. Even though patients of different racial or ethnic backgrounds cannot receive consistent results, impaired phagocyte clearance of immune complexes is a significant pathogenetic mechanism in SLE. Additionally, a recent study found that SLE patients have impaired non-inflammatory engulfment phagocytosis of apoptotic cells [71]. Apoptotic waste that circulates continuously may act as an antigen for the development of immune complexes as well as an immunogen for the induction of autoreactive lymphocytes. Pathogenic autoantibodies in SLE are produced and secreted as a result of the interaction between CD4 and CD8 helper T cells and double negative T cells (CD4 and CD8 with B cells) [72]. As a result, cells like NK cells and CD8 suppressor T cells that typically prevent B cell activation from occurring are defective in this regard. It has been demonstrated that CD8 T cells and NK cells from SLE patients with active disease frequently fail to inhibit the synthesis of polyclonal immunoglobulins and autoantibodies. A recent study found that SLE patients with active disease had impaired CD8 T suppressor cell function [73]. One factor that contributes to the disease's persistence could be the B cells' impaired suppression.

Environmental Activators

Although genetic predisposition and hormonal environment may contribute to SLE, the disease is likely caused by several exogenous and environmental triggers. Toxins and drugs alter cellular reactivity and immunogenicity of self-antigens, infectious agents induce specific responses through molecular mimicry and disrupt immune regulation, nutrition affects the production of inflammatory mediators, physical/chemical agents such as ultraviolet (UV) induce inflammation, induce apoptosis, tissue damage. The effects of these environmental triggers on susceptible individuals may vary greatly with varying periods of disease onset and remission, which may be another explanation for the heterogeneity of the disease.

- **Chemical and Physical Factors**

Many medicines, including procainamide and hydralazine, which are aromatic amines or hydrazines, can cause a lupus-like syndrome, especially in people who are genetically slow acetylators [74]. Aromatic amines, hydrazines, and their derivatives are present in a large number of substances used in commercial, industrial, and agricultural applications. Additionally, tobacco and tobacco smoke contain hydrazine naturally. People who have consumed or come into contact with these agents have been reported to develop lupus-like syndromes [75]. Aromatic amines, which are present in permanent hair coloring products, can be absorbed through the scalp. The induction and exacerbation of both cutaneous and systemic lupus erythematosus have been linked to exposure to sunlight, a well-known environmental factor. Many SLE patients have significant triggers, particularly UVB light [76].

- **Infectious diseases and dietary factors.**

No one dietary factor or infectious agent has consistently been proven in more than one study, despite the fact that they are both implicated in the pathogenesis of SLE. Several case reports [77] have suggested a connection between consuming L-canavanine-containing alfalfa sprouts and the emergence of lupus-like symptoms. Theoretically, viruses and other infectious agents can start or exacerbate SLE by activating B cells, inflicting tissue damage that releases autoantigens, and molecularly mimicking the disease. The presence of viral "footprints" in the tissues of SLE patients has not, however, always been proven.

- **Environment-wide estrogens.**

The consumption of meat and dairy products from livestock that have been given synthetic oestrogen feed is thought to increase human exposure to environmental oestrogens over time [79]. Oestrogens are also being used more frequently for contraception and by postmenopausal women. In prepubescent non-immune mice, chronic oestrogen exposure has been shown to affect thymic development and subsequently immune tolerance [78]. Therefore, it is conceivable that fetal exposure to oestrogenic substances could pose a risk to the development of the immune system. A slight rise in the risk of developing SLE has also been linked to HRT and the use of OC pills. Therefore, in people who are susceptible, environmental oestrogens and endocrine disrupting substances may be significant autoimmunity triggers.

CLINICAL MANIFESTATIONS

Multiple systems are affected by SLE, which has a wide range of symptoms [80]. Fatigue is one of the most prevalent symptoms and is present in 80–100% of patients. This has been linked to the disease activity as well as other complications like anemia or hypothyroidism, suggesting that it is likely multifactorial [81]. Lupus complications have the potential to be fatal [82,83]. A few of these are:

i. Constitutional manifestations: Patients with SLE can have a variety of systemic manifestations. Fever, malaise, arthralgia, myalgia, headache, loss of appetite and weight loss are some common symptoms. In new cases or recurrent episodes of active SLE, the most common symptoms are nonspecific fatigue, fever, arthralgia, and weight changes. The most common physical symptom of SLE is fatigue, which can be caused by active SLE, medications, lifestyle choices, concurrent fibromyalgia, or affective disorders. In most cases, other clinical and laboratory markers also appear with fatigue brought on by active SLE. Another frequent but vague symptom of SLE is fever, which can have a variety of causes, the most frequent of which are infection, drug fever, and active SLE. To distinguish between these, careful history-taking may be helpful. In people with active SLE, weight loss is possible. Additionally, corticosteroid therapy or an active illness like nephrotic syndrome anasarca may cause weight gain [84]. These signs and symptoms can be mistaken for fibromyalgia, chronic fatigue syndrome, infectious diseases, endocrine disorders, and other autoimmune diseases [85].

ii. LN, or lupus nephritis: In the majority of patients, LN is present. Children with lupus experience renal involvement more frequently than do adults [86]. Maintaining a high index of suspicion is important, and signs like swelling in the extremities, headache, vision changes, and weight gain should raise suspicions about renal involvement. Physicians treating patients should routinely screen for hematuria, proteinuria, and clinical and laboratory indicators for the development of nephrotic syndrome and hypertension [87]. In most cases, microscopic hematuria and proteinuria appear before more obvious clinical signs of nephritis. Persistent deterioration of renal function, recurrent proteinuria, and active urinary sediments are common. Each institution has its own criteria for when a kidney biopsy should be performed to assess the severity of the disease [88].

iii. Pulmonary manifestations: Pleurisy, pleural effusion, interstitial pneumonia, pulmonary infarction, pulmonary hypertension, pneumonia, and hemorrhage are common pulmonary manifestations in children with SLE [89]. Periodic surveillance should be performed because many patients have subclinical lung disease and abnormal pulmonary function tests [90]. In immunocompromised patients with pulmonary symptoms, pneumonia and other infections should be considered and ruled out immediately.

iv. Cardiac manifestations: Children with lupus frequently have pericardial disease, myocardial disease, valvular disease, coronary artery disease, and heart failure among other cardiac abnormalities. A significant amount of morbidity may not be present before cardiac disease manifests itself, and it frequently starts out silent. As many as 68 percent of children with lupus have abnormal echocardiograms, according to studies [90]. The most frequent cardiac symptom in children with lupus is pericarditis, which may be correlated with anti-Ro and anti-La antibodies [91]. Patients may not exhibit any symptoms at all or they may experience chest pain, dyspnea, tachycardia, and low-grade fever. Antiphospholipid antibodies may or may not be related to clinical myocarditis, which is less common, and valvular heart disease [92].

v. Hematologic Symptoms: Each of the cell lines can be impacted by the various hematologic symptoms of SLE. Children with SLE frequently exhibit anemia, leukopenia, and thrombocytopenia. Anemia and leukopenia are particularly prevalent in diseases that are not well controlled and may be indicators of disease activity [93]. According to the association between chronic disease and anemia, the latter is more common. In children, thrombocytopenia may be the first sign of SLE, and in our experience, it may appear many years before other symptoms do. Anemia, leukopenia, thrombocytopenia, and antiphospholipid syndrome (APS) are the main symptoms of systemic lupus erythematosus. In a study of 126 SLE patients, 45% had neutropenia, 27% had thrombocytopenia, 20% had lymphopenia, and 13% had hemolytic anemia [2,3]. The American College of Rheumatology (ACR) classification criteria for SLE list the most common manifestations of SLE, although they vary greatly between patients. This includes leukopenia and hemolytic anemia with reticulocytosis, leukopenia [4,5].

vi. Splenomegaly and lymphadenopathy: About 50% of SLE patients experience lymph node enlargement. The onset of the illness or exacerbations are when it is more frequently observed. Lymphadenopathy can also result from infection or a lymphoproliferative condition like angioimmunoblastic T cell lymphoma, which is characterized by arthritis, Coombs' positive hemolyticanemia, skin rash, fever, and weight loss [9]. 10–46% of patients develop splenomegaly, especially when the disease is active. As seen during a pathologic examination of the spleen, the splenic arteries have an onion-skin appearance, which is thought to be a healed vasculitis lesion. Given that SLE patients have a four to five-fold increased risk of non-Hodgkin lymphoma, it is important to take into account the possibility of lymphoproliferative malignancy [9].

vii. Musculoskeletal illness associated with systemic lupus erythematosus: Children with SLE frequently develop arthritic conditions like myositis and avascular necrosis. Commonly affecting the small joints in the hands and feet, arthritis is typically non-deforming. Myositis is visible but difficult to distinguish from myopathies brought on by steroids or other drugs [94]. Myositis associated with SLE activity is suggested by the presence of proximal muscle weakness along with elevations in the muscle enzymes and acute phase reactants. Muscle enzymes are frequently normal in steroid myopathy cases, and there is little laboratory data to support worsening disease activity [94]. Avascular necrosis is a well-known side effect of corticosteroid therapy and is unpredictably influenced by the dosage or length of corticosteroid therapy.

viii. Gastrointestinal manifestations: Mouth ulceration is a common symptom of SLE. The American College of Rheumatology uses eleven criteria to classify SLE, and one of them is oral ulceration. People with SLE frequently experience gastrointestinal symptoms related to their primary SLE as well as negative drug side effects [93]. Since bowel infarction, mesenteric vasculitis, peritonitis, and pancreatitis can all be caused by active lupus, abdominal pain in SLE is important. Patients with active SLE frequently experience nausea and dyspepsia, which can be challenging to link to objective signs of gastrointestinal involvement [94]. Autoimmune hepatitis-related jaundice can also happen. Patients with SLE frequently experience gastrointestinal symptoms, which can be brought on by underlying gastrointestinal conditions, side effects of treatment, or even SLE itself [95]. The liver is not usually considered the primary target organ of injury in patients with SLE because abnormal liver function is not part of the diagnostic criteria for the disease. Lupus hepatitis, although rarely, causes mildly elevated levels of the liver enzymes aspartate transaminase [AST], alanine transaminase [ALT], lactate dehydrogenase [LDH], and alkaline phosphatase, usually in the presence of active lupus [96]. The liver is the main organ affected by lupus hepatitis, which is a unique condition. A serological distinction is usually possible between lupus hepatitis in the presence of anti-ribosomal P and dsDNA autoantibodies, and in the latter case in the presence of anti-smooth muscle and auto liver-kidney-mitochondria (LCM) antibodies. [96,97].

ix. Vascular manifestations: Information on its vascular manifestations is scarce. Peripheral vascular disease has grown in

importance as a cause of morbidity as lupus patients live longer. At the beginning of SLE, one-third of patients experience Raynaud's phenomenon. Ischemic or ulcerated fingers are uncommon in SLE patients. Fingers, toes, ears, noses, and even the tongue can be impacted by Raynaud's phenomenon. Inflammatory vascular disease, such as vasculitis, can also occur in SLE patients. Vasculitis in SLE is caused by the complex interaction of immune cells, endothelial cells, autoantibody tangles, and immune complexes.

x. Ocular manifestations: Lupus' ocular symptoms are a reflection of the underlying illness. The presence of ocular manifestations should inform the clinician that disease activity is probably present elsewhere. Keratoconjunctivitis sicca (KCS), which affects approximately 25% of patients, is the most typical ocular symptom of SLE. Less frequently occurring eye conditions include conjunctivitis, interstitial keratitis, episcleritis, and diffuse or nodular scleritis [96]. Episcleritis and scleritis can have symptoms that closely resemble systemic disease in terms of their severity. Rarely do SLE patients develop necrotizing scleritis. After KCS, retinal involvement in SLE is the second most frequent ocular manifestation. The cotton-wool spot, a defining feature of lupus retinopathy, has been linked to avascular zones on fluorescein angiography. Infiltration of vessel walls with fibrillar material, which results in vascular constriction and widespread hyaline thrombus formation, is one of the histopathological findings [97].

xi. Obstetric manifestations: In patients with SLE, the pregnancy outcome seems to be worse. Fetal deaths in utero rise in proportion to SLE. SLE during pregnancy increases the risk of spontaneous abortion, stillbirth, or fetal retardation [95]. Anticardiolipin antibody and lupus anticoagulant, two closely related lupus autoantibodies, have now been found to be related to miscarriage risk. Blood tests can identify these autoantibodies, which are present in one-third to one-half of lupus-suffering women. Pregnancy ought to be timed during a period of disease remission [95]. Neonatal lupus, which is brought on by maternal antibodies crossing the placenta and may be another side effect of SLE during pregnancy, affects roughly 3% of infants born to mothers with SLE [98].

xii. Endocrine manifestations: 3–24% of patients with SLE also have autoimmune thyroid disease, which is more common in patients with SLE than in the general population and may have a genetic basis [99]. There is controversy as to whether SLE is an independent risk factor for thyroid disease, or whether young and middle-aged women at greatest risk for SLE also have autoimmune thyroid disease [99]. Patients with lupus can develop type 1 and type 2 diabetes, but this is less common [100]. Lupus patients have an unexpectedly high rate of fractures - five times higher than the general population.

DIAGNOSIS OF SLE

The method for determining whether a patient has SLE is based on the idea that specific outlined haematological symptoms must appear clinically. This is specifically used in our environment as an early method of diagnosis to suspect the disorder. However, caution must be exercised to rule out additional hematological conditions, especially infectious diseases and hematological malignancies, both of which can result in positive Anti-nuclear antibody (ANA) tests.

SLE hematological markers

- **Anaemia:**

Hemoglobin levels define it as a common hematologic abnormality in SLE. Anemia of chronic disease (ACD) is the most common type (60-80%), iron deficiency anemia (IDA), autoimmune hemolytic anemia (AIHA) and anemia due to chronic renal failure. ACD is caused by chronic inflammation that suppresses erythropoiesis (normocytic and normochromic, low to normal serum iron, adequate bone marrow iron stores, elevated serum ferritin). This is common and may be associated with menorrhagia or increased gastrointestinal blood loss due to long-term corticosteroid use. IDA is defined as a serum ferritin level below 20 g/dl [8]. Symptoms of AIHA include a high reticulocyte count, low haptoglobin, elevated indirect bilirubin, and a positive direct Coombs test.

- **Leucopenia:**

It is a typical SLE symptom that can be brought on by lymphopenia, neutropenia, or a combination of the two. Between 20 and 81 percent of SLE patients have lymphopenia, and the severity of the condition may be correlated with the severity of the illness. Natural killer cells are typically elevated while Tand B lymphocytes are decreased [9]. Leucopenic patients with SLE have been shown to have decreased surface expression of the complement regulatory proteins CD55 and CD59.

- **Neutropenia.**

Anti-neutrophil antibodies may play a role in mediating this common SLE feature, which has a prevalence rate of 47%. Through excessive neutrophil apoptosis-mediated neutropenia, elevated levels of TNF-related apoptosis-inducing ligand (TRAIL) in SLE may cause neutropenia [15]. Additionally, it might be caused by drugs like immunosuppressives, NSAIDs, or intermittent medications other than corticosteroids.

- **Decreased Eosinophils and basophils:**

Low absolute eosinophil and monocyte counts can result from steroids. Additionally, basophil counts may fall in SLE, especially when the disease is active [9].

- **Thrombocytopenia.**

The most likely pathogenic mechanism is increased peripheral platelet destruction coupled with anti-platelet antibody presence. In SLE, thrombocytopenia can be acute in onset, extremely severe, and responsive to corticosteroids. The chronic form is more prevalent, less likely to be caused by disease activity, and typically less responsive to steroid therapy.

- **Pancytopenia.**

It might be brought on by bone marrow failure, as in the case of aplastic anemia. SLE has been associated with macrophage activation syndrome, despite it being unusual. Anemia, leukopenia, hyperferritinemia, anti-DNA antibodies, low CRP, fever, weight loss, arthritis, pericarditis, rash, myocarditis, nephritis, splenomegaly, hepatomegaly, lymphadenopathy, and myocarditis are some of its symptoms.

PERCEPTION OF SLE IN NIGERIA

The lack of disease registries and the scarcity of epidemiological data are significant barriers to comprehending disease characteristics, incidence, prevalence and building a solid SLE knowledge base in Nigeria. However, Adelowo *et al.* found polyarthritis to be the most prevalent presentation of SLE, occurring in 5.28 percent of 1250 rheumatic cases seen over a 6-year period in Southwest Nigeria [107]. Anemia, Leucopenia, Lymphopenia, Thrombocytopenia, and Elevated ESR are the main hematological findings that SLE patients typically exhibit. Another study carried out by Airenakho *et al* has demonstrated that in Nigerians with SLE, renal involvement may occur earlier and progress more severely [108].

According to recent data and experience from several medical and diagnostic centers in Africa, SLE is becoming more common in black Africans, contrary to earlier beliefs that it is uncommon. The apparently low incidence of previously reported SLE may be attributed to low disease detection, particularly in primary health care, limited access to testing facilities, underdiagnosis due to limited access to health services, and shortage of specialists. The majority of physicians suspect other diagnoses based on the physical symptoms they observe and the hematological findings without the confirmatory test of ANA, making misdiagnosis a significant challenge in our environment [107].

In Nigeria, hydroxychloroquine (HCQ), aspirin, and steroids are the first lines of treatment for SLE, due to its accessibility and affordability. However, second or third-line medications are not commonly used because patient pay out-of-pocket, high cost of drugs, and inadequate NHIS coverage [108].

TREATMENT OPTIONS

The prognosis of SLE is fatal and requires a multidisciplinary approach. An all-inclusive approach involving supportive and definitive treatment can also reduce long-term morbidity and

mortality. Currently, the use of bisphosphonates in children remains controversial due to insufficient information on their long-term safety and potential teratogenicity [115].

SLE medications can be divided into three main categories:

1. First-line medications include Aspirin, Steroids, and Hydroxychloroquine.
2. Immunosuppressive medicines like Methotrexate, Mycophenolate Mofetil, Azathioprine, Cyclophosphamide, and Voclosporin are second-line medications.
3. Biologic medications like Belimumab and Rituximab are third-line medications.

These agents are usually used in combination but the first line agents are known increase the risk of infections and myelosuppression [102]. Failure of the first line drugs or unwanted side effects would lead to the introduction of second or third line drugs either singly or in combination.

The symptoms of each patient's specific case of SLE have a major impact on the course of treatment. According to the latest recommendations of the European League against Rheumatism for the treatment of SLE, patients without significant organ manifestations can be treated with antimalarial and/or glucocorticoids. Alternatively, short-term NSAIDs can be used cautiously in patients who are not at high risk of complications. In addition, immunosuppressive drugs such as azathioprine, mycophenolate mofetil, and methotrexate should be considered in patients with SLE who are unresponsive to or unable to reduce corticosteroid doses below long-term safe doses [103].

Belimumab is a newer and safer treatment option which was approved by the USFDA in 2011 for the treatment of SLE in adults only. It is an IgG1y monoclonal antibody that inhibit the activity of soluble cytokine BLyS (B lymphocyte stimulator) or B-cell activating factor (BAFF). It has been shown to reduce autoantibody levels in patients with SLE and help control disease activity [104].

Another biologic agent, Rituximab, a monoclonal antibody that binds to CD20 on the surface of B cells and destroys it. However, despite the ability of rituximab to deplete B cells that that of Belimumab, randomized control trials of rituximab in SLE failed to reach their primary clinical endpoint, whereas the primary clinical endpoint were reached in 4 independent phase III clinical trials of Belimumab in SLE. Unfortunately, in our environment these drugs are not readily available and accessible due to their cost [105,106].

CONCLUSION

We can attribute the low prevalence of SLE in low resource economy to difficulty in effectively diagnosing SLE with the current health infrastructure available in most centres leading to misdiagnosis in most cases.

To arrest this situation, the following are recommended to aid early detection of SLE; Physicians should have a high index of suspicion when patients present with the following hematological results (Anemia PCV<30, Leucopenia <4000/µl, Lymphopaniea <1000/µl, Thrombocytopenia <100,000/µl and Elevated ESR >20mm/1st hour). In terms of treatment regimens employed, it is imperative that newer treatment techniques such as the biologic agents should also be considered in extreme cases. Seminars, presentations and Hospital grand rounds should be carried out frequently to re-educate, build and strengthen capacity of physicians on SLE. Government should invest in health and increase the NHIS insurance coverage by making more affordable, accessible diagnostic and treatment options. Creative approaches such as public health sensitization should be encouraged. Finally, larger studies involving multi-center approach across the geo-political zones should be carried out.

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