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Systemic Lupus Erythematosus: contributory factors and diagnosis.

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Abstract: *Systemiclupus erythematosus (SLE) an autoimmune disease more common in women and those of African,Caribbean and Chinese descent. Genetic and drugs have important role in the disease. SLE has abnormalities in apoptosis (a programmed cell death).SLE is"the great imitator" it oftenmimics or is mistaken for other illnesses. Common chronic complaints include fever, malaise, jointpain, muscle pain and fatigue. Neuropsychiatric syndromes can result after SLE affects CNS or peripheral nervous system. Common neuropsychiatric manifestations of SLE include cognitive dysfunction, mood disorder, cerebrovascular disease, seizure, polyneuropathy, anxiety disorder, psychosis, depression, and in some extreme cases personality disorder. Pregnancy outcome appears to be worse in people with SLE whose disease flares up during pregnancy. Thediagnostic criteria of American college of Rheumatology(ACR)is useful. Treatment includes corticosteroids and anti-malarial drugs. Intravenous immunoglobulins may be used to control SLE with organ involvement or vasculitis. No cure is available for SLE but treatments for the disease. Over 90% survive for more than 10 years*

Keywords: *SLE,Role of genetic, Clinical manifestation, Prognosis.*

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I. Introduction

Systemic lupus erythematosus(SLE) or as Lupus. Lupus a Latin words for "wolf" and "erythro" a Greek for "red". All explanations originate with the reddish, butterfly shaped rash around the nose and cheeks [1,2] Rate of SLE varies between countries from 20 to 70 per 10,000[3].Women of childbearing age are affected about nine times more often than men[4].Those of African, Caribbean, and Chinese descent are at higher risk than white people[4].SLE is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue in many parts of the body [1].The cause of SLE is not clear[2]It is thought to involve genetics together with environmental factors [4].Among identical twins, if one is affected there is 24 % chance that other one will be as well[1].Female sex hormones, sunlight, smoking, vitamin D deficiency, and certain infections, are also believed to increase the risk[4].There are a number of other kinds of lupus erythematosus including discoid lupus erythematosus, neonatal lupus, and subacute cutaneous lupus erythematosus[2]Common symptoms include painful and swollen joints, fever, chestpain, hairloss, mouthulcers, swollen lymph nodes, feelingtired, and a red rash which is most commonly on the face [2]. Diagnosis can be difficult and is based on a combination of symptoms and laboratory tests [2]There is no cure for SLE[2]. Treatments includes NSAIDs, corticosteroids, immunosuppressant's,hydroxychloroquinine, andmethotrexate [2]Alternative medicine has not shown to affect the disease [2].Life expectancy is lower among people with SLE [5,].SLE increases the risk of cardiovascular disease with this being the most common cause of death [4].With modern treatment about 80% of those affected survive more than 15 years [6].Women with lupus have pregnancies that are higher risk but mostly successful;[2].The paper reviews the current concepts on SLE.

II. Worldwide prevalence

The global rates of SLE are approximate 20-70 per 10,000 people. In females rate is highest between 45-64 years of age. The lowest overall rate exists in Iceland and Japan. The highest rates exist in US and France .however; there is no sufficient evidence to conclude that SLE is less common in some countries compared to others, since there is significant variability in these countries. For example different countries receive different level of sunlight, and exposure to UV rays affects dermatological symptoms of SLE. Certain studies hypothesize that racial composition of countries effects disease, and will cause the incidence in a country to change as the racial makeup changes. In order to understand if this is true, countries with homogenous and racially stable

populations should be studied to better understand incidence [3].Rates of incidence in developing world are unclear [7].The rate of SLE varies between countries, ethnicity, and sex,and changes over time[3].In the United States, one estimate of the rate of SLE is 53 per 100,000[8].Other estimates range from 322,000 to over 1 million [8].In the Northern Europe the rare is about 40 per 100,000 people [9].SLE occurs more frequently and with greater severity among those of non-European descent[9].That rate has been found to be as high as 159 per 100,000 among those of Afro-Caribbean descent [8].Childhood onset systemic lupus erythematosus generally presents between the ages of 3 and 15 and is four times more common in girls [10].While the onset and persistence of SLE can show disparities between genders, socioeconomic status also plays a major role. Women with SLE and of lower socioeconomic status have been shown to have higher depression scores, higher body massindex, and more restricted access to medical care than women of higher socioeconomic statuses with the illness. People with SLE had more self-reported anxiety and depression scores if they are from lower socioeconomic status [11].

Role of ethnicity:There are assertions that race affects the rate of SLE.However, a 2010 review of studies which correlate race and SLE several sources of systematic and methodological error, indicating that the connection between race and SLE may be spurious [12].For example studies show that social support is a modulating factor which buffers against SLE-related damage and maintains physiological functionality[12].Studies have not been conducted to determine whether people of different racial backgrounds receive different levels of social support [12].If there is difference, this could act as a confounding variable in studies correlating race and SLE .Another caveat to note when examining studies about SLE is that symptoms are often self-reported. This process introduces additional sources of methodological error. Racial differences in lupus progression have not been found in studies that control for the socioeconomically status (SES) of the participants,[12].However, the severity of symptoms and mortality are both similar in white and non-white patients. Studies that report different rates of disease progression in late-stage SLW are most likely reflecting differences in socioeconomic status and the corresponding access to care [12].People who receive medical care have often accrued less disease-related damage and are less likely to be below poverty line [13].Additional studies have found that education, marital status, occupation, and income create a social context which contributes to disease progression [12].

Role of gender:SLE like many autoimmune diseases affects females more frequently than males, at a rate of about 9 to one [5,8].The X chromosome carries immunological related genes, which can mutate and contribute to the onset of SLE.The Y chromosome has no identified mutations associated with autoimmune disease [14].In addition to hormonal mechanisms, specific genetic influences found on the X chromosome may also contribute to the development of SLE.Studies indicate that the X chromosome can determine the levels of sex hormones. A study has shown an association between Klinefelter syndrome and SLE syndrome and SLE.XXY males with SLE have an abnormal X-Y translocation in the partial triplication of PAR1 gene region [15].

III. Contributory Factors

Role of genetic: SLE is presumably caused by a genetic susceptibility coupled with an environmental trigger which results in defects in the immune system. One of the factors associated with SLE is vitamin D deficiency [16].Research indicates SLE may have a genetic link.SLE does run in families, but no single casual gene has been identified. Instead multiple genes appear to influence a person's chance of developing lupus when triggered by environmental factors. LA class 1,class II,and class III genes are associated with SLE,but only classes I and II contribute independently to increased risk of SLE [17].Other genes which contain risk variants for SLE are IRF5¸PTPN22,STAT4 [18,wp,46].CDKN1A [19].ITGM,BLK [18].TNFSF4 andBANK1 [20].Some of the susceptibility genes may be population specific [18].While the genetics of SLE are not very well understood, there is growing evidence for the involvement of specific genes in this complex autoimmune disease. The part of the complexity of this disease is due to the effects of both environment and genetics factors that may contribute to its development [21].Further compounding our understanding of the etiology of the disease is the involvement of several organ system. [22].

Genetic studies of the rates of disease in the families support the genetic basis of this disease with a heritability of >60% [23].Identical (monozygotic) twins were found to share susceptibility to the disease at > 35% rate compared to fraternal (dizygotic) twins and other full siblings who only showed a 2-5% concordance in shared inheritance [23].SLE is regarded as a prototype disease due to the significant overlap in its symptoms with other autoimmune diseases [22].This means that it is an important area of continued research and study that is utilizing diverse technologies such as GWAS ,mircroarrys,and murine studies[23].Further genetic studies of multiple ethnic groups and the creation of disease models incorporating environmental influences will help to increase and refine the understanding of specific genes, linkages, as well as the mechanisms underlying the disease. [23].

Role of drugs: Drug induced SLE is a (generally) reversible condition that usually occurs in people being treated for a long- term illness. Drug induced lupus mimic SLE .However symptoms of drug- induced lupus

disappear once the medication that triggered the episode is stopped. More than 38 medications can cause this condition, the most common of which are procainamide, isoniazid, hydralazine,quinidine,andphenytoin[24]. Dermatologic-Discoid(cutaneous) lupus is limited to skin symptoms and is diagnosed by biopsy of rash on the face, neck scalp or arms .Approximately 5% of people with DLE,progress to SLE [25].

IV. Disease progression

One manifestation of SLE is abnormalities in apoptosis, a type of programmed cell death in which aging or damaged cells are neatly disposed as a normal growth or functioning. In SLE, the body's immune system produces antibodies against itself, particularly against proteins in the cell nucleus. SLE is triggered by environmental factors that are unknown. Immune system must balance between being sensitive enough to protect against infection, and become sensitized to attack the body's own protein (autoimmune).During an immune reaction to a foreign stimulus, such as bacteria, virus, or allergen cells that would normally be deactivated due to their affinity for self-tissues can be abnormally activated by signaling sequences of antigen presenting cells. Thus triggers may include viruses, bacteria, allergens (IgE and other hypersensitivity),and can aggravated by environmental stimulants, such as ultraviolet light and certain drug reactions. These stimuli begin a reaction that leads to destruction of other cells in the body and exposure of their DNA, histones, and other proteins, particularly parts of the cell nucleus. The body's sensitized B lymphocyte cells will now produce antibodies against these nuclear related proteins. These antibodies clump into antibody complexes which stick to surfaces and damage blood vessels in critical areas of the body, such as the glomeruli the kidney; these antibody attacks are the cause of SLE.Researchers are now identifying the individual genes, the proteins they produce, and their role in immune chain, and researchers are trying to find drugs to break each of those links [26,27].SLE is a chronic inflammatory disease believed to a type III hypersensitivity response with potential type involvement [28].Reticulate and stellate acral pigmentation should be considered a possible manifestations of SLE and high titers of anti-cardiolipin antibodies or a consequence therapy [29].

Malfunction of cell death and cell clearance: Apoptosis (cell death) is increased in monocytes and keratinocytes. Expression of Fas by B cells and T cells in increased. There are correlations between the apoptotic rates of lymphocytes and increase activity. Necrosis is increased in T lymphocytes.Tangible body macrophages (TBMs)-large phagocytic cells in the germinal centers of secondary lymph nodes-express CD68 protein. These cells normally engulf B cells that have undergone apoptosis after somatic hyper maturation. In some people with SLE,significantly fewer TBMs can be found and these cells rarely contain material from apoptotic B cells.Also,uningested apoptotic nuclei can be found outside of TBMs.This material may present a threat to the tolerization of B cells and T cells. Dendritic cells in the germinal center may endocytose such antigenic material and present it to T cells, activatingthem. Also apoptotic chromatin and nuclei may attach to the surfaces of folicullar dendritic cells and make this material available for activation other B cells that may have randomly acquired self-specificity through somatic hyper maturation [30].Necrosis, a pro-inflammatory form of cell death is increased in T lymphocytes, due to mitochondrial dydfunction,oxidativestress, depletion of ATP [31].

SLE is associated with defects in apoptotic clearance, and the damaging effects caused by apoptotic debris. Early apoptotic cells "eat me",of cell –surface protein such as phosphotidyserin^{e},that prompt immune cells to engulf them. Apoptotic cells also express "find me" signals, toattract macrophages and dendritic cells. When apoptotic material is not removed correctly by phagocytes, they are captured instead by antigen-presenting cells,which leads to development of antinuclear antibodies [4].

V. Clinical Manifestations

SLE is one of several diseases known as "the great imitator" because it often mimic or is mistaken for other illnesses [32].SLE is a classicalitem in differential diagnosis[26].Common initial and chronic complaints includes fever, malaise, jointpains, musclepains, and fatigue. Because these symptoms are so often seen in association with other diseases, these signs and symptoms are part of the diagnostic criteria for SLE.When occurring in conjunction with other signs and symptoms, however they are considered suggestive [33]..While SLE can occur in both males and females, it is found far more often in women, and symptoms associated with each sex are different [5].Females tend to have a greater number of relapses, a low blood cell count, morearthritis, Raynaud'sphenomena, and psychiatric symptoms. Males tend to have more seizures, kidney disease,serositis (inflammation of tissues lining the lungs and heart),skin problems, and peripheral neuropathy [34].

External and internal organ involved: Asmany as 70% of people with lupus have some skinsymptoms. Three main categories of lesions are chronic cutaneous (discoid) lupus, subacute cutaneous lupus, and acute cutaneous lupus. People with discoid lupus may exhibit thick, red scaly patches on the skin. Similarly, subacute cutaneous lupus manifest as red scaly patches of skin but with distinct edges.Acute cutaneous lupus manifest as rash. Some

have classic malar-rash(or butterfly rash) associated with the disease [35].This rash occurs in 30 to 60% of people with SLE [36].Hair loss, mouth and nasal ulcers, and lesion on the skin are other possible manifestations [37].

The most commonly involved sought medical attention is for joint pain, with small joints of the hand and wrist usually affected, although all joints are at risk. More than 90 percent of those affected will experience joint or muscle pain at some time during the course of illness [38]Unlike rheumatoid arthritis, lupus arthritis is less disabling and usually does not cause severe destruction of the joints. Fewer than ten percent of people with lupus arthritis will develop deformities of the hands and feet [38].People with SLE are at particular risk of developingosteoarticular tuberculosis [39].A possible association between rheumatoid arthritis and SLE has been suggested [40], and SLE may be associated with increased risk of bone fractures in relatively in young women [41].

Anemia is a common in children with SLE [42],and develops in about 50% of cases [43].Low platelet and white blood cell counts may be due to the disease or side effect of pharmacological treatment. People with SLE may have an association with antiphospholipid antibody syndrome [44],(a thrombotic disorder),wherein autoantibodies to phospholipids are present in their serum. Abnormalities associated with antiphospholipid anybody syndrome include a paradoxical prolonged partial thromboplastic time (which usually occurs in hemorrhagic disorders) and positive test for antiphospholipid antibodies; the combination of such findings have earned the term "lupus anticoagulant positive ".Another antibody finding in SLE is the anti-cardiolipin antibody,which can cause a false positive test for syphilis.

SLE may cause pericarditis- inflammation of the outer lining surrounding the heart, myocarditis-inflammation-of heart muscle, orendocarditis's-inflammation of inner lining of the heart. The endocarditis of SLE is non-infectious, and is also calledLibman-Sacks endocarditis).It involves either the mitral valve or the tricuspid valve. Atherosclerosis also occurs more often and advances more rapidly than in general population [45].Inflammation of the pleurae known as pleurisy can rarely give rise to shrinking lung syndrome [46].SLE can cause pleuritic pain and also give rise to shrinking lung, involving reduced lung volume [47].Other associated lung conditions include pneumonitis, chronic diffuse interstitial lung disease, pulmonaryhypertension, pulmonaryemboli, and pulmonary hemorrhage[47].

Painless passage of blood or protein in the urine may often the only presenting sign of kidney involvement. Acute or chronic renal impairment may develop with lupus nephritis, leading to acute or end stage kidney failure. Because of early recognition and management of SLE,end-stage renal failure occurs in less than 5% [48].The histological hallmark of SLE is membranous glomerulonephritis with "wire-loop" abnormalities [49].This finding is due to immune complex deposition along the glomerular basement membrane, leasing to a typical granular appearance in immunofluorescence testing.

Neuropsychiatric syndromes can result when SLE affects central or peripheral nervous system. The American College of Rheumatology defines 19 neuropsychiatric syndromes in systemic lupus erythematosus [29].The diagnosis of neuropsychiatric syndromes concurrent with SLE(now termed as NPSLE)[50],is one of the most challenges in medicine, because it can involve so many different patterns of symptoms, some of which may be mistaken for signs of infectious disease or stroke [51].A common neurological disorder people with SLE have is headache, although the existence of a specific lupus headache and optimal approach to headache in SLE remain controversial [52,53,].Other common neuropsychiatric manifestations of SLE include cognitive dysfuction, mooddisorder, cerebrovascular disease [52],seizure, polyneuropathy, anxiety disorder,psychosis, depression, and in some extreme cases personality disorder [52].

Neurological disorders contribute to a significant percentage of morbidity in people with SLE [54].As a result, the neural side effect of lupus is being studied in hopes of reducing morbidity and mortality rates [50].One aspect of this disease is the severe damage to the epithelial cells of the blood- brain barrier in certain regions, depression affects up to 60% of women with SLE [55].

SLE causes an increased rate of fetal death in utero and spontaneous abortion (miscarriage).The overall live-birth rate in people with SLE has been estimated to be 72% [56].Pregnancy outcome appears to be worse in people with SLE whose disease flares up during pregnancy [57].Neonatal lupus is the occurrence of SLE symptoms in an infant born from a mother with SLE, most commonly presenting with rash resembling discoid lupus erythematosus, and sometimes systemic abnormalities such as heart block or enlargement of the liver and spleen [58].Neonatal is usually benign and self-limiting [59].Fatigue in SLE is probably multifactorial and has been related to not only disease activity or complications such as anemia or hyperthyroidism, but also to pain, depression, poor sleep quality, poor physical fitness and lack of social support [59].

VI. Diagnosis

Antinuclear antibody (ANA) testing and anti-extractable nuclear antigen (Anti-ENA) form the mainstay of serologic testing for SLE.Clinically most widely used method id indirect immunofluorescence (IF).The pattern of fluorescence suggests the type of antibody present in people's serum. Direct

immunofluorescence can detect deposits of immunoglobulins and complement proteins in people's skin. When skin not exposed to the sun is tested, a positive direct IF (the so-called lupus band test) is an evidence of systemic lupus erythematosus [60].

Diagnostic criteria: The American College of Rheumatology (ACR) established eleven criteria in 1982 [61], which were revised in 1997 as a classificatory instrument to operationalize the definition of SLE in clinical trials. They were not intended to be used to diagnose individuals and do not do well in that capacity. For purpose of identifying people for clinical studies, a person has SLE if any 4 out of 11 symptoms are present simultaneously or serially on two separate occasions [62], that includes: a)Malar rash(rash on cheeks),ensitivity 57;specificity=96% [63],b)Discoid rash, sensitivity =18%,specificity=99% [63],c),Serositis: pleurisy,lung and heart involvement, sensitivity=56%;specificity=85%(pleural is more sensitive, cardiac is more specific)[63].d)Oral ulcers, sensitivity=27%;specificity=96% [63].e)Arthritis nonneosive arthritis of two or more peripheral joints, with tenderness, swelling, oreffusion, sensitivity 86% and specificity 37% [63].f) Photosensitivity (exposure to ultraviolet light causes rash, or other SLE flare-ups),sensitivity 43%,specificity 96%, g)Blood-hematologic disorder-hemolytic anemia,leukopenia, lymphopenia or low platelet count in the absence of offending drug sensitivity 59% ,specificity 89% [63]..Hypocomplementemia is also seen due to either consumption of C3 and C4 by immune complex induced inflammation or to congenitally complement deficiency, which may predispose to SLE [64].h)Renal disorder: more than 0.5 g per day protein in the urine or cellular casts seen in urine under a microscope, senility 51%,specificity 94% [63].i).Antinuclear antibody test positive; sensitivity 99 %,specificity 49% [63].j).Immunologicdisorder: Positive anti-Smith, antiDNA, antophospholipid antibody or false positive serological test for syphilis; sensitivity 85%, specificity 93 % [63],.Presence of anti-ss DNA in 70% of cases(though also positive with rheumatic disease and healthy person) [65]. k)Neurologic disorder: seizure or psychosis; sensitivity 20%,specificity 98% [63].Other than the ACR criteria people with lupus may also have :fever (over 100 F/37.7 C,extremefatigue, hairloss, and finger turning white or blue when cold(Raynaud's phenomenon)[66].

VII. Treatment and Prognosis

Treatment can include corticosteroids and anti-malarial drugs. Certain types of lupus nephritis such as diffuse proliferative glomerulonephritis require intermittent cytotoxic drugs. These drugs include cyclophosphamide and mycophenolate. Hydroxychloroquine was approved by FDA for lupus in 1955 [67].Some drugs are approved for other diseases are used for SLE'offlevel'. InNovember 2010,an FDA panel recommended approving belimumab(Benlysta) as a treatment for pain and flare-ups common in lupus. The drug was approved by FDA in March 2011 [68].Disease modifying ant- rheumatic drugs (DMARDs) commonly in use are antimalarial such as hydroxyl chloroquine and immunosuppressant's (e.g.metotrexate and azathioprine).Hydroxychloroquine has relative few side effects, and ther is evidence that it improves survival among people who has SLE [67].

In more severe cases, medications that modulate the immune system (primarily corticosteroids and immunosuppressant) are used to control the disease and prevent recurrence of symptoms. Depending on the dosage, people who require steroids may develop Cushing's syndrome, which may include obesity, puffy round face, diabetesmellitus, increasedappetite, difficulty sleeping and osteoporosis. Long term use of even low doses can cause elevated blood pressure and cataracts. New drugs target the responses of individual immune cells. Some of these drugs are already FDA approved for treatment of rheumatoid arthritis [67].Potent NSAIDs such as indomethacin and diclofenac are relatively contraindicated for people with SLE because they increase the risk of kidney failure and heart failure [67]

Intravenous immunoglobulins may be used to control SLE with organ involvement, orvasculitis. It is believed that they reduce antibody production or promote the clearance of immune complexes from the body [69].Avoiding sunlight in SLE is critical, since sunlight is known to exacerbate skin manifestations of the disease. Avoiding activities which induce fatigue is also important. Drugs unrelated to SLE should be prescribed only when known not to exacerbate the disease. Occupational exposure to silica, pesticides,and mercury can also worsen the disease [70].Kidney transplants are treatment of choice for end stage kidney disease and lupus nephritis but recurrence of full disease is common in up to 30% of people [71].Approximately 20% of people with SLE have clinically significant antiphospholipid antibodies, which are associated with antiphospholipid syndrome. If this disorder is suspected, brain scans are usually required for early detection. Low doses of of anticoagulants e.g., aspirin is prescribed, warfarin are used for cases involving thrombosis [72].

SLE and pregnancy:While most infants born to mother who have SLE are healthy, pregnant mothers with SLE should remain under medical care until delivery. Neonatal lupus is rare, but identification of mothers at highest risk for complications allows for prompt treatment before or after birth. In addition, SLE can flare up during pregnancy, and proper treatment can maintain the health of the mother longer. Women pregnant to have anti-Ro(SSA) or anti-La antibodies (SSB) often have echocardiograms during the 16^{th} and 30^{th} weeks of

pregnancy to monitor the health and surrounding vasculature. Contraception and other reliable forms of pregnancy prevention is routinely advised for women with SLE, since getting pregnant during active disease was found to be harmful. Lupus nephritis was the most common manifestation [73].

Prognosis: No cure is available for SLE but there are treatments for the disease [1].In the 1950s, most people diagnosed with SLE lived fewer than five years. Today over 90% survive for more than 10 years, and many live relatively symptom free,80-90 % can expect to live a normal lifespan [74].Mortality rates are however elevated compared to people without SLE[75].Prognosis is typically worse for men and children than for women,however, if symptoms are present after 60,the disease tends to a more benign course Early mortality within 5 years, is due to organ failure or overwhelming infections, both of which can be altered by early diagnosis and treatment [67].To reduce the potential for cardiovascular issues, high blood pressure and high cholesterol should be prevented or treated aggressively. Steroids should be used at the lowest dose for shortest possible period, and other drugs that can reduce symptoms should be used whenever possible [67].

VIII. Conclusions

Despite the advancement in treatment there is no cure for SLE.AnAutoimmune disease where the body's immune system attacks healthy tissue in many parts of the body. New drugs target the responses of individual immune cells. Strong NSAIDs are relatively contraindicated due to the risk of kidney failure and heart failure. Prognosis is worse for men and children than women. Steroids to be used at the lowest dose for shortest possible period

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