Etiological Components and Patterns Contributing to the Development of Systemic Lupus Erythematosus

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Abstract

Intro: Systemic Lupus Erythematosus (SLE) is a multisystem inflammatory autoimmune disease that affects more than a quarter million people in the United States today. It involves a dysfunction within the humoral immune systems that leads the body to attack its own tissues mediating a chronic disease comprising episodes of exacerbations and remissions in which severe complications may occur.

Background: Although the exact etiology of SLE is unknown, previous research has implicated a multitude of etiological components associated with SLE including genetic, hormonal, immunologic and environmental influences. In fact, research has found the development of SLE dependent upon the interaction of these components. The current literature review seeks to examine the underlying patterns and interactions of etiological components that contribute to the development of SLE.

Methods: The following databases were used in completing searches: Google, Scholar, Pub Med (n=9), Europe PMC (n=8) and Wiley Online Library (n=2). Additionally, ancestry searches were used to locate articles (n=8).

Results: Various factors were identified under each etiological category contributing to SLE. There is a prominent gene-environmental interaction that often triggers the disease and the hormonal-gene and gene-immunologic interactions are more often thought to progress the disease leading to further dysfunction of the immune system.

Discussion: These results highlight the complexity and need of etiological interactions for SLE to develop. Despite the varying ways for the disease to begin, identification of susceptible genes for targeted gene therapy could lower the risk of SLE development. Further research is necessary to identify etiological components and corroborate the extent of interaction for SLE to develop.
Introduction

According to the Centers for Disease Control and Prevention ([CDC], 2018), SLE affects approximately 1 in every 2000 persons which amounts to relatively 250,000 to 350,000 people in the United States. SLE primarily presents in women during the reproductive age with a ratio of 90 women to 10 men. The interaction of the identified four etiological categories-hormones, genes, immunology, and environment- results in a large production of autoantibodies or antibodies against self-antigens, as well as immune complexes, which target all organ systems in the body (Huether & McCance, 2016). The wide selection of targeted tissues and cellular components enables numerous and diverse manifestations such as stroke, glomerulonephritis, leukopenia, alopecia or reproductive abnormalities. Complications alike these cause drastic, long term altercations in quality of life emotionally and physically (Huether & McCance) (Lewis et.al. 2017). While treatments are available, many are inadequate (Gough & Simmonds, 2007). Due to the severity of this disease process, lack of cure and effective treatments, understanding the etiology, prophylactic interventions and therapy are a necessity (Gough & Simmonds, 2007). Further research is necessary to corroborate each etiological component and its role in the development of SLE. More specifically, limited work has examined the patterns of etiologic components that trigger the production of defective antibodies and hence SLE. With identification of these patterns, there is greater potential for prophylactic therapies to evolve. Therefore, the current literature review seeks to investigate underlying etiological components and interactional patterns contributing to the development of SLE.
Methodology

In identifying studies to be included in this literature review, articles/studies related to the subject of interest were examined. The following databases and search engines have been used in completing searches: Medline, PubMed, Nursing Reference Center Plus, Google, Scholar, Europe PMC and Wiley Online Library (n=2). Additionally, ancestry searches were used to locate articles (n=8). Additional information was sought from Health Source: Nursing/Academic Edition. Ancestry and Key phrase searches were methods utilized to locate the intended articles. Criteria for article selection were evaluated upon citations, publisher/author, and subject relevance and content.

Review of Literature

Genetic Influences

The study by Molokhia and McKeigue (2005) reported that risk for SLE increases with specific ethic origins. The prevalence of general lupus was found to be higher within African-American, Afro-Caribbean, Native American, Asian Indian, Polynesian and Chinese populations in comparison to populations of primarily European descent. The consistent higher prevalence of lupus in these ethnic populations despite their living in different environments supports the conclusion that genetic factors are involved within the pathology of SLE. The specific genes or genetic factors that increase risk through ethnicity have not been identified nor related to varying allele frequencies known to be associated with SLE risk.

One genetic factor that has been identified involves the HLA region, more specifically the HLA-DR2 and HLA-DR3 genes. As discussed by Gough & Simmonds (2007), the HLA region has been strongly associated or correlated with autoimmune diseases for approximately fifty years now. It is responsible for encoding cellular components and molecules that have
significant roles in the immune system. The molecules generated from this region influence the antigen presentation to CD4+. The CD4+ is a type of T lymphocyte cell referred to as the T-helper cell, because it releases cytokines, which initiate the body’s response to a perceived threat or pathogen. This is significant in understanding autoimmune disease initiation and progression. It has a clear relation to SLE, as the body’s inability to recognize its self-antigens is what leads the immune system to faultily identify itself as a threat and subsequently attack its own tissues and cellular components.

**Hormonal Influences**

Estrogen has been identified as one factor that may contribute to the development of SLE (Lewis et.al. 2017). Lang (2004) reports that while estrogen’s role in the sex differences of SLE remain unclear, estrogen has been found to have immunomodulatory effects. These effects extend to regulation of lymphocyte survival and expansion of all T lymphocyte cells (Khan & Ansar Ahmed, 2016). Much research today has demonstrated that estrogen has the ability to increase the number of plasma cells, which are responsible for producing antibodies also known as immunoglobulins (Khan & Ansar Ahmed, 2016). Additionally, estrogen can specifically enhance the production of autoantibodies. These effects of estrogen account for women during reproductive years being found to have the highest prevalence of SLE. It also explices why the prevalence rates slowly equalize with men as age increases or menopause occurs. This is further supported by statistical reports of increased onset, exacerbations and worsening symptoms when estrogen levels are high. These situations may occur naturally through menarche and pregnancy or artificially through use of oral contraceptives (OC) (Lewis et.al. 2017) (Sanchez-Guerrero, Karlson, Liang, Hunter, Speizer, & Colditz, 2005).
Although, the effect of oral contraceptives has been shown to have a minor effect. Sanchez-Guerrero and his colleagues (2005) designed and implemented a prospective cohort study in which 121,645 women who used oral contraceptives in the past were followed over fourteen years. The study overall examined the relationship between past OC use and development of SLE. Specific elements studied with this relationship included the duration of OC use and the period from first use. No association or correlational relationships were identified from this data. Although, the researchers overall found and concluded there is a small but increased risk of developing SLE from past OC use compared to persons who have no OC use. The study “Shingles, allergies, family medical history, oral contraceptives, and other potential risk factors for systemic lupus erythematosus” (1994) additionally supported that oral contraceptives have an “extremely modest” affect in contributing to the development of SLE.

Environmental Influences

As discussed by Molokhia and McKeigue (2005), the contribution of environmental factors to SLE are not fully understood. Though, past research has identified specific elements that have been associated with it including the following: ultraviolet light, smoking, stress, toxins, infections, occupational exposures and certain drugs that increase oxidative stress (Barbhaiya & Costenbader, 2016). As these are exposures that many people encounter daily, research suggests that true risk does not occur unless an individual has genetic susceptibility to SLE (Vaillant, 2020). The susceptibility or predisposition to SLE implicates that an individual has a set of genetic variations that increase their risk of acquiring the disease by contributing to its origination but not directly causing it (NIH Genetics Home Reference, 2020). Thus, when these environmental elements encounter or interact with susceptible genes, the risk for acquiring SLE increases or activation may occur (Vaillant, 2020).
More over infections that trigger SLE, they are typically reported as viral. One specific virus of important mention is the Epstein Barr Virus (EBV). The connection between EBV and Lupus continues to perplex researches today as it produces an unusual response in comparison to other viral infections in which the patients have irregular cytokine production as well as impaired CD8+, which release toxic substances to destroy identified pathogens (James & Robertson, 2012). Overall however, EBV has multiple roles as a potential etiology of SLE and more research is needed for understanding. Drug induced SLE also has multiple mechanisms that can be unique to each drug. Approximately 40 medications have been recognized as a potential trigger of SLE. The most frequently reported include procainamide, hydralazine and quinidine (Lewis et.al, 2017). Other chemical or toxic exposures include mercury, solvents and pesticides. These were shown to have significantly contributed to the development of SLE in agricultural and dental workers. The researchers concluded there is strong association for these occupational exposures, though did warn that the data may be influenced by a smaller sample size and low prevalence (Cooper et. al, 2004). Crystalline silica, a common exposure to agricultural workers has also been identified as a risk factor. It enables SLE development by increasing inflammation and antibody production ((Parks et al., 2002). Additionally, a study conducted in North Georgia also revealed environmental pollution as a potential risk factor. Kardestuncer and Frumkin (1997) examined the prevalence and incidence of lupus in an African-American community that experienced long term exposure of industrial emissions. The results of the study corroborated their hypothesis that the prevalence would be higher among that population in comparison to other communities.

**Immunologic Influences**
In normal function, when a cell is damaged it to pursue healing or repairment. In cases that repairment fails, the cell then initiates a programmed self-destruction, a process known as apoptosis (Vaillant, 2020). During this process, internal proteins known as self-antigens are displayed on the surface of the apoptotic cell so that it may be consumed by a mononuclear phagocyte cell. When the products are not cleared effectively, nucleic acids or proteins are exposed to the immune system and the body in reaction becomes sensitized to the self-antigens through B and T lymphocyte activation (Vaillant, 2020). In response, various autoantibodies are produced such as the Anti-nuclear-antibodies (Lewis et.al. 2017). When the body encounters these materials again, cytokine release, the complement activation system, and production of autoantibodies are all stimulated (Vaillant, 2020). Circulating immune complexes then lead to further tissue and organ damage from the resulting inflammatory processes of complex deposits in organ membranes and tissues (Lewis et.al. 2017). This inflammatory reaction to the complexes is considered an immunologic factor that contributes to the development of SLE because it progresses or advances the state of disease and damage (Midgley).

Another immunologic factor to highlight as a contributing element to SLE development is the defective clearance of apoptotic material (Midgley). SLE patients have been found to have a deficiency of the compliment proteins, specifically C1, C2, C3 and C4, which enable and promote the macrophages ability to clear apoptotic material effectively (Vaillant, 2020).

**Discussion and Summary**

Systemic lupus erythematosus is a chronic autoimmune disease, with multisystemic involvement. The pathophysiology of SLE is suspected to begin with injury to the body’s cells, consequently resulting in damaged DNA and cellular proteins. This initial damage generally occurs through any environmental exposures as discussed previously. The environmental risk
factors are considered the activating factor or trigger of SLE. Genetic predisposition and specific hormones have a pre and post-affect in which they lower the body’s tolerance to self-antigens and increase the body’s likelihood of acquiring the disease. The immunologic and hormonal components interact in unclear pathways today to sustain and potentially advance the disease condition. While exact patterns and the extent of each etiological category have not been defined in their contribution to SLE development, researchers have identified the interactions among the four primary etiologies and the pursuit of understanding for these etiologies remains vastly unwavering. The results of studies revealed that upon further investigation, gene therapy and correction of immune deficiencies are potential prophylactic therapies.

Limitations of this literature review include lack of similarity between all procedural and design methods; lack of a unanimous standard of information provided in addition to small sample sizes, varying age ranges, and lack of repetition for these studies to verify results. Another considerable limitation of the studies appeared to be the lack of assessment for the extent of exposure to risk factors and the total summation of risk factors pre-diagnosis. Further research should explore these elements and continue to investigate the patterns in which these etiological categories interact to develop SLE.
References


