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Review Article

Poorly understood pathogenesis of Systemic Lupus Erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease and as we know immune system is vast and complex and presents an enormous challenge to scientists working in this field as well as presents a challenge to anyone seeking to explain where pathogenesis research stands at the end of 2011. Because of this vast and complex nature of immune system the pathogenesis of SLE is incompletely defined and understood. The aim of this study is to highlight areas of differences among researchers in explaining pathogenesis of systemic lupus erythematosus so as to clear the confusion in future researches so as to bring a degree of uniformity. This uniformity is vital to gain full understanding of the disease so as to design therapies that might ameliorate harmful effects of this disease.

1. Introduction

An autoimmune disorder like SLE is a growing problem worldwide due its complex aetiology and pathogenesis. Genetic and exogenous factors such as the stress, trauma, drugs and environmental toxins are associated with pathogenesis of SLE. Often linked to hormonal imbalances and chronic inflammation that stress the immune system and cause improper immune responses. These improper immune responses are directed to the endogenous normal cells and tissues. Pathogenic mechanisms are poorly understood. Nonetheless, increasing evidence suggests that many of these illnesses result from large number of factors in genetically susceptible individuals.

Lupus is a life-altering and life-threatening disease" says Catherine Madden, Executive Director of Lupus Canada. "This incurable disease impacts and destroys many organs in the body. Lupus is seriously fatal disease, but dedication to new research fuels our hope for a cure. Known as the "disease with 1000 faces, its symptoms vary so greatly from person to person. The symptoms of lupus often mimic other illnesses, and it can attack any tissue or organ in the body including skin, muscles, joints, blood and blood vessels, lungs, heart, kidneys and the brain. Common and often chronic symptoms of lupus include joint pain and inflammation, skin rashes, sun sensitivity, extreme fatigue, fever, chest pain and hair loss. Because of the varied symptoms, lupus can be extremely difficult to diagnose.

Review criteria

This review highlights different contradictory research results that form the basis why there is no complete cure of the disease. These include the complexity of the disease itself; the lack of reliable outcome measures; our limited understanding of the pathogenesis of the disease; the propensity of lupus patients to have bad outcomes and to react to medicines in unusual ways; the heterogeneity of the patient population; the unpredictable course of disease in individual patients; and the lack of reliable biomarkers. I systematically searched number of articles, webpages, and major textbooks for pathogenesis of SLE. All papers identified were English-language, full manuscripts. I also searched the reference lists of identified articles for additional relevant papers.

Differences in research results

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease [1]. There are controversies and lack of understanding in the pathogenesis of systemic lupus erythematosus. Autoantibodies are formed in systemic lupus erythematosus that react with self antigens of the body. Number of challenges and controversies persist concerning their origin, clinical usefulness and relevance [2].

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The role of IL-6 in the pathogenesis of SLE is also controversial. Some authors found elevated IL-6 levels in cases with increased C-reactive protein, concluding that it is part of the acute phase response, [3]. However others found high levels in the cerebrospinal fluid in cases with CNS involvement-3.Many authors reported that serum TNF a - is clearly elevated and was found to correlate with SLE disease activity, [4] others reported increased levels only in a minority of patients with active SLE that correlates with thrombocytopenia.

There is also silicone breast implant controversy associated with SLE. Studies of systemic lupus erythematosus (SLE) and systemic sclerosis did not show an association with silicone breast implants, but studies of symptoms did [5-10]. Because of a lack of consistency in methodology of symptom searches and in study findings some reviewers do not believe there is fire to be found [11]. Since then, a Dow Corning-funded study and documented that 28 symptoms were increased in silicone patients [5]. In a comparison study, there was a statistical correlation between local problems and systemic problems. Despite so many studies, there is no scientific evidence that definitively links silicone or saline breast implants with connective tissue or autoimmune diseases such as lupus. Stress such as surgical procedures can trigger lupus flares, so this must be factored into the assessment of risk and benefits of the procedure.

Some authors have reported specific headache disorder in patients suffering from SLE [11]. Critics of this concept argue that there are no quality studies showing that headaches in patients with SLE differ from those in the general population. A detailed definition of the term lupus headache is lacking, since the terms "severe" and "persistent" are not quantified. Headache due to lupus requires evidence of a disease flare accompanying the headache, and resolution of the headache with immunosuppressant treatment. However, a meta-analysis found no correlation between headaches and disease activity [12].

An additional frustration relates to the fact that many of the symptoms of lupus are the sorts of aches, pains, and fatigue that are common among people who don't have lupus. People with lupus are, therefore, faced with further uncertainty: Is their symptom related to lupus, or can it be chalked up to aging or a completely unconnected ailment? SLE is accompanied by several features that can be attributed to involvement of the central or peripheral nervous system. The aetiology and pathogenesis of these manifestations are mostly unknown. To which degree these neuropsychiatric conditions can be explained on the basis of chronic illness, or as part of the disease spectrum of SLE, is also a matter of debate.

Better understanding of the pathogenesis of cerebral lupus will come from the study of experimental models, as it has been possible to develop an antiphospholipid antibody syndrome in mice.

Because no specific laboratory test for CNS lupus is yet available, diagnosing the condition remains a challenge to every clinician. Techniques including neuropsychometric testing, quantitative EEG, and SPECT scans have taught us more about cognitive dysfunction and psychosis in patients with SLE. These categories remain the most difficult to define [13].

In the present literature there is still controversy as to whether patients with SLE are at increased risk of developing malignant diseases. In recent years a number of epidemiological studies have been conducted and some have suggested an association between SLE and malignant diseases while other studies have not [14].

One of the hallmarks of SLE is the loss of tolerance to chromatin. The genes and mechanisms that trigger this loss of tolerance remain unknown [15].

One important feature of this disease is a strong female predominance with female to male ratio of approximately 9:1 [16]. This ratio is reduced in pre-adolescent and post-menopausal females, suggesting a critical role for sex hormones [17-18] .Studies have shown that female sex hormones including oestrogen increase the incidence and severity of disease whereas loss of oestrogen and/or the addition of androgens alleviate or reduce clinical features of the disease. To date it remains unclear what cellular events distinguish the female immune response from the male immune response resulting in this sex-based disparity [17].

Shrinking lung syndrome (SLS) is an infrequently reported manifestation of systemic lupus erythematosus (SLE). However Pathogenesis is not fully understood [19]. Clearly SLE is a largely genetically based, as has been apparent for a number of decades based on identical twin studies [20]. Nevertheless, these important advances have so far not allowed us to clarify the underlying pathogenic mechanisms. Thus, the genetic analyses, in their complexity, have failed to give us clear directions for targeted therapy development.

What else then contributes to disease development, beyond the underlying genetic risks? The textbooks always list environment as an important factor, but in fact only UV light has been generally accepted as a contributing element, although recent data also suggest that a nearly–ubiquitous virus, EBV, might also play a facilitating role [21- 26].

There is a paradoxical role for complement in lupus pathogenesis. On one hand, active disease is associated with activation of the classical complement pathway [27, 28]. It is generally believed that autoantibodies within circulating immune complexes fix and activate complement, contributing to tissue damage. Similarly, in murine models of the disease IgG2a autoantibodies are of particular importance to disease pathology because of their ability to fix complement [29]. Conversely, it has

been shown that individuals with a homozygous deficiency in components of the classical pathway of complement activation are at increased risk of developing SLE. Specifically, individuals who are homozygous deficient for the C1 complex proteins (C1q, C1r, or C1s), and C4 have a greater prevalence of disease and develop a more severe disease [30, 31]. Individuals deficient for C2 are at greater risk for SLE, though less so than those deficient in C1 or C4 [32]. Additionally, other health conditions that result in very low complement levels may predispose individuals to SLE [33]. It is not clear how complement can have these two contradictory roles in lupus pathogenesis.

To make matters even worse, not only are lupus patients complicated, diverse, and difficult to predict, but as a group they seem to respond differently to new therapies. Our experience with rituximab is illustrative [34, 35].

Current Research Questions

The development of several novel compounds has been pursued for lupus, but so far nothing has been proven to be curative.

The reason being poorly understood pathogenesis of SLE as noted in the above studies.

It requires significant additional research efforts and dedicated resources over an extended period; this will eventually provide the understanding of pathogenesis of SLE and ultimately enable the cure of the disease.

Key Messages

· Immune system is vast and complex and presents an enormous challenge to scientists working in this field.

· SLE is auto-immune disease with thousands of faces of presentation; Pathogenesis of SLE is not clearly understood as evident in this article.

· Unanimous opinion regarding is pathogenesis is father needed in future

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