Childhood-Onset Systemic Lupus Erythematosus: A Review and Update

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Lupus is a chronic, autoimmune multisystem inflammatory disease that is associated with sizable morbidity and mortality.[1] When lupus commences in an individual less than 18 years of age,[2] it is commonly referred to as childhood-onset systemic lupus erythematosus (cSLE). With a reported incidence of 0.3-0.9 per 100 000 children per year, and a prevalence of 3.3-24 per 100 000 children,[3] cSLE is rare. About 10%-20% of all patients with SLE are diagnosed during childhood. Typically, cSLE has a more severe clinical course than that seen in adults, with a higher prevalence of lupus nephritis, hematologic anomalies, photosensitivity, neuropsychiatric, and mucocutaneous involvement.[3-5]

As with adult-onset SLE, a higher frequency of cSLE has been described in African Americans, Asians, Hispanics, and Native Americans compared with whites.[6,7] The median age at presentation is around 11-12 years, with cSLE rarely reported under the age of 5 years.[8] Consistent with adult-onset disease, cSLE has a strong female preponderance; the female to male ratio is at 4:3 and 4:1 for disease onset in the first and second decades of life, respectively.[9]

In this review, we provide an update on cSLE, focusing on information deemed especially relevant to general pediatricians in their role of caring for children and adolescents with this disease. Neonatal and drug-induced lupus are not discussed.

Pathogenesis of Lupus

The etiology of cSLE is multifactorial, involving genetic risk factors, epigenetic mechanisms, and environmental triggers.[10-13] Systemic Lupus Erythematosus (SLE) is thought to constitute a loss of tolerance in a genetically susceptible individual with progression to autoimmunity that is triggered by various environmental factors and infections[14] (**Figure 1**).

ACR	American College of Rheumatology
ANA	Antinuclear antibody
AZA	Azathioprine
cSLE	Childhood-onset systemic lupus erythematosus
CYC	Cyclophosphamide
EBV	Epstein-Barr virus
GC	Glucocorticoid
HCQ	Hydroxychloroquine
Ig	Immunoglobulin
MMF	Mycophenolate mofetil
NPSLE	Neuropsychiatric manifestations of SLE
PJP	*Pneumocystis jirovecii* pneumonia
QI	Quality indicator
SLE	Systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinic

Genetic Factors

There is a 10-fold increase in SLE risk among monozygotic as compared to dizygotic twins.[15,16] Further, siblings of a patient with SLE carry an 8- to 20-fold higher risk of developing SLE as compared with a healthy general population.[16,17]

SLE is considered a polygenic disease, although rare monogenic causes have been described recently.[18] Genetic variants that are well-established include very rare mutations in genes coding for select complement factors. Indeed, a single gene mutation that results in a complete deficiency of C1q increases the risk of SLE, or lupus-like symptoms, to more than 90%. C4 deficiency is also a well-established risk factor for the disease and a lower number of copies of the C4 gene increases the risk of cSLE.[19] Genome-wide association studies have identified a series of additional risk alleles that have the potential to influence the function of both the innate and the adaptive immune systems.[20] However, genetic predisposition alone does not account sufficiently for the risk of developing SLE, given that the concordance rate among monozygotic twins is approximately 40%.[17,20]

Environmental/Epigenetic Factors

Epigenetic factors also contribute to the development and manifestations of SLE.[20,21] Ultraviolet light, especially ultraviolet B,[22] infections,[23] and toxins are all suspected to promote the onset and exacerbation of SLE.[6,16] There is an increasing body of evidence suggesting that at least some environmental triggers exert their influence through epigenetics. These triggers seem to alter the degree of DNA methylation and the phosphorylation of histones, leading to a change in gene transcription rates without modifying the gross genetic structure of the DNA itself.[21,24] SLE has been associated with reduced DNA methylation in gene regions that can promote loss of B- and T-cell tolerance.[21,25,26] Prolonged exposure to ultraviolet light increases the amount of self-antigen presented to the immune system via free DNA in the blood owing to destruction of dermal cells; abnormal apoptosis and/or structural alterations in DNA of dermal cells increase their immunogenicity.[27,28]

Epstein-Barr virus (EBV) is another proposed inducer and enhancer of tolerance loss. In individuals with a genetic susceptibility for SLE, EBV infections lead to marked B-cell activation that results in the production of large amounts of

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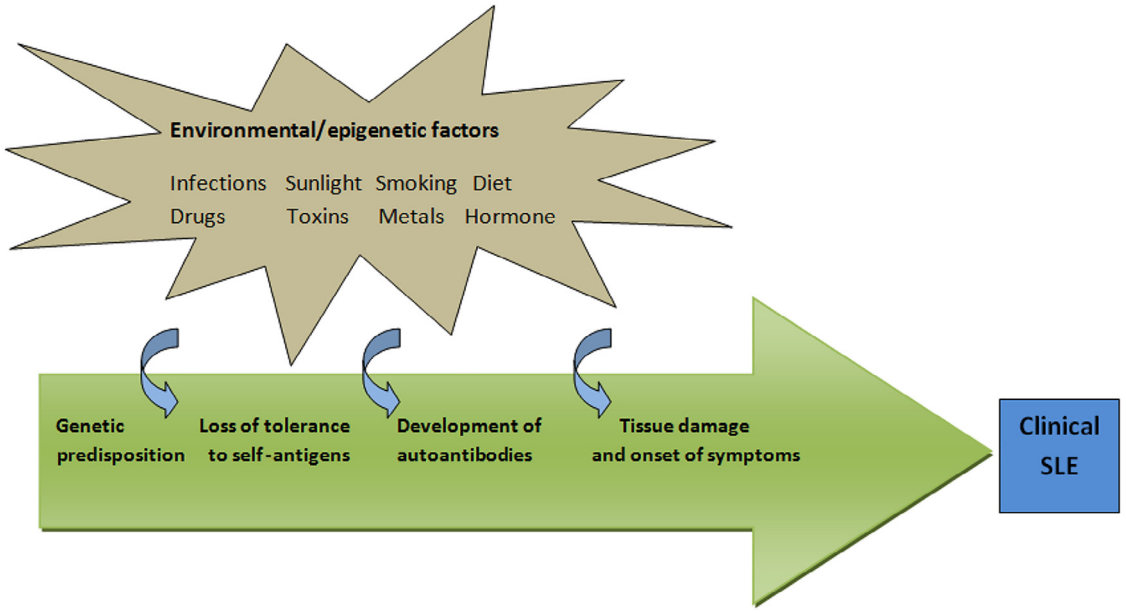

Figure 1. Loss of self-tolerance causing the production of autoantibodies in a genetically susceptible individual causing clinical SLE.

autoantibodies, which in turn can further a loss of tolerance.[23,29-31] Given the high frequency of EBV infections in the population as compared with the relative rarity of SLE, EBV infections alone are unlikely the only infectious trigger of SLE.[16,23,32]

As such, silica, allergens, and certain cosmetics all have been associated with SLE in certain ethnic groups.[16] However, strong scientific evidence regarding the mechanisms that result in SLE upon exposure to these toxins is lacking at present.

Hormones

Compared with age-matched males, SLE is 8-15 times more common in females in their reproductive years.[33] The higher prevalence of SLE in females suggests that genes on the X chromosomes, estrogen, or other sex hormones may promote SLE manifestations.[6,17] Indeed, estrogen prolongs the lifespan of autoreactive lymphocytes,[34-36] and mutations on the X chromosome have been associated with SLE.[37,38]

Immune Dysfunction in SLE

SLE is characterized by the production of antibodies against self-antigens, many years before the onset of overt signs or symptoms of SLE in adults. In up to 85% of patients with SLE, autoantibodies precede initial clinical symptoms by an average of 2-3 years, with prodromal periods as long as 9 years described in some individuals.[16,17,39]

Antinuclear antibodies (ANAs) are formed first, followed by anti–double-stranded DNA, antiphospholipid antibodies, and anti-Smith and anti-ribonucleoprotein.[16,40] The respective autoantigens escape the regulatory mechanisms of the immune system, resulting in the production of these autoantibodies and resultant overproduction of proinflammatory cytokines.[16,17,39,41] Further, autoantibodies lead to dysregulation of both the innate and adaptive immune systems, including the formation of immune complexes that are associated with the development of tissue damage.[6,17,20,22,23]

Clinical Presentation of Disease

There is often a delay in diagnosis ranging from 1 month to 3.3 years, given the nonspecific and highly variable initial presentations with cSLE.[42] At disease onset, there is often a combination of fever, weight loss, arthralgia or arthritis, a photosensitive and/or malar rash, and renal disease.[43] Presenting features of cSLE are acute, commonly involving many organs at diagnosis. Compared to adults, children often experience a more severe clinical course of cSLE.[4,5,44,45] **Table I** provides a summary of the frequency of clinical signs and symptoms at initial presentation in cSLE.

Constitutional Symptoms

Fever, weight loss, malaise, fatigue, and lymphadenopathy are the most frequent constitutional symptoms with cSLE, both at presentation and over time.[43] Understandably, none of these symptoms are specific to cSLE; other disease processes including infections and malignancy need to be excluded.

Mucocutaneous Symptoms

Skin involvement is exceedingly common with cSLE both at diagnosis and during the course of the disease. The most typical cutaneous manifestation is the fixed eruption of the so-called butterfly rash or malar rash (**Figure 2**). Besides often painless oral and nasal ulcers, nonscarring alopecia also is often observed, typically in the frontal area.[8,9,46,47] Different from adults, an isolated discoid lupus rash is rare in children.