Updates on Childhood-Onset SLE

Essay

Submitted for partial fulfillment of master degree
in **Pediatrics**

Presented by

Mohamed Ibrahim Abdelmawla
(M.B.B.CH.) 2008
Faculty of Medicine – Ain Shams University

Under Supervision of

Prof. Khaled Salah Awwad
Professor of Pediatrics
Faculty of Medicine – Ain Shams University

Dr. Zeinab Ebraheem Hasan
Assistant Professor of Pediatrics
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
2013


بسم الله الرحمن الرحيم
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ
صدق الله العظيم
سورة البقرة آية (٣٢)

LIST OF CONTENTS

LIST OF ABBREVIATIONS

Abs	: Antibodies
ACR	: American collage Of Rheumatology
Ag	: Antigen
ANA	: Antinulcear antibodies
apLS	: Antiphosphelpid antibodies
AVA	: Avuscular necrosis
AZA	: Azathioprine
CBC	: Complete blood count
CD	: Cluster of differentiation
CMV	: cytomegalovirus
CNS	: Central nervous system
DLE	: Discoid lupus erythematosus
DM	: Diabetic mellitus
DNA	: Deoyribometric acid
dsDNA	: Double stranded deoxyribonucleic acid
EBV	: Epstein-Barr virus
ESRD	: End stage renal disease
FBC	: Full blood count
GFR	: Glomerular filtration rate
HLA	: Human leucocytic antigen
IFN	: Interferon
Ig	: Immunoglobulin
IL	: Interleukin
JDAM	: Juvenile dermatositis
JIA	: Juvenile idiopathic arthritis

MMF : Mycophenolate mofetil
Msk : Musculoskeletal
NSAIDs : Non steroidal anti-inflammatory drugs
PCR : Polymerase chain reaction
PD : Programmed cell death
PMN : Polymorph nuclear neutrophil
PSLE : Pediatric systemic lupus erythromatosus
RBC : Red blood cell
SCLE : Subacute cutaneous lupus erythematosus
SLE : Systemic lupus erythematosus
SNP : single nucleotide polymorphisms
STAT : Signal transducer and activities of transcription
UV : Ultraviolet
WBCs : White blood cells
WHO : Wold Health Organization

LIST OF TABLES

Table No. *Page No.*

LIST OF FIGURES

Figure No. *Page No.*

Introduction

Systemic lupus erythematosus in children and adolescents (pSLE) is a multisystem autoimmune disease with a great variability in disease presentation and course. The diagnosis of systemic lupus erythematosus (SLE) is based on the clinical and laboratory features consistent with this illness in the absence of another autoimmune disease that could explain the findings. At time of diagnosis of pSLE, most but not all patients have at least four of the American College of Rheumatology Classification Criteria for SLE ***(Benseler and Silverman, 2005).***

Diagnosis of SLE requires maintaining an appropriate index of suspicion; in this regard, it is helpful to remember the general demographics and epidemiology of SLE. A recent study comparing long-term outcomes between adult- and childhood-onset lupus provides the age of onset data of a large cohort of patients living in the United States. The mean age of onset of 795 adult-onset patients was 36.5 years, whereas the age of onset of 90 childhood-onset patients was 14 years ***(Hersh et al., 2009).***

The up to 20% of SLE patients who are diagnosed during childhood, i.e., prior to age 16 years, tend to experience a more severe disease course than those with disease onset later in life ***(Hiraki et al., 2008).***

Early diagnosis and treatment of SLE can prevent disease flares as well as potentially irreversible damage to major organs such as the kidneys, lungs, heart, or nervous system. Although there are many atypical presenting syndromes that may result in significant delays in diagnosis, most patients present with more easily recognizable disease patterns including joint pain and swelling, facial rash and/or photosensitivity, pleuritic or pericardial chest pain, Raynaud phenomenon and persistent fatigue, and fever or weight loss ***(Lam and Petri, 2005).***

Aim of the Work

The purpose of this review is:

1. To describe manifestations of **SLE** in children.
2. To describe recent mode of diagnosis and investigations of **SLE** in children.
3. To summarize recent data on new therapeutic modalities for **SLE** in children.

Chapter (1)
Overview of SLE in Children

Historical Background:

The word *lupus* means wolf in Latin, as the destructive injuries the disease caused brought to mind the bites of this animal ***(Holubar, 1980)***. The earliest usage of the term *lupus* in the English literature is in the 10th century biography of St. Martin, written in 963 AD. However, Hippocrates is generally considered the first to have described cutaneous ulceration; calling it herpes esthiomenos, which means, gnawing dermatosis ***(Mallavarapu and Grimsley, 2007).*** Any process involving ulceration or necrosis of the lower limbs or face was loosely labeled lupus before the mid-19th century ***(Fatovic-Ferencic and Holubar, 2004)***. The first clear description of lupus erythematosus is credited to Laurent Theodore Biett of the Paris School of Dermatology, who called it erythema centrifugum ***(Smith and Cyr, 1988).*** The butterfly rash was recognized in 1845, and in 1852 the term *lupus erythemateux*was coined. Osler described the clinical features, and in 1924 Libman and Sacks reported the characteristic endocarditis. In 1948 Hargroves and colleagues described the lupus erythematosus (LE) cell and one year later cortisone was first used. In 1957 the association of a positive ANA and SLE was made ***(Silverman and Eddy, 2011).***

Etiology and Pathogenesis:

Developing a model of SLE pathogenesis is challenging, given the need to account for tremendous heterogeneity in disease expression and fluctuations of disease activity over time.

Environmental factors

It is likely that lupus is a combination of genetic susceptibility and environmental factors, including exposure to sunlight, infections, drugs, and chemicals. Patients with SLE have a high incidence of drug allergies. Drug-induced lupus is a well-recognized form of SLE. Exposure to many chemicals, including hair dye, tobacco, L-canavanine, and other environmental factors have been associated with SLE ***(Cooper et al., 2009).***

In some patients exposure to ultraviolet radiation, and in particular ultraviolet (UV)-B rays, may exacerbate either skin or systemic disease. In vitro studies have shown that exposure of cells, and particularly keratinocytes, to UV radiation leads to apoptosis, allowing blebs containing autoantigens to appear on the cell surface, which can then be processed and lead to an autoimmune response ***(Silverman and Eddy, 2011).***

Viral infections, including parvovirus B19 and cytomegalovirus (CMV), are common in patients with SLE.Studies of adults with SLE have demonstrated that a significantly higher percentage of patients had exposure to Epstein-Barr virus (EBV) than did those in a control group ***(Silverman and Eddy, 2011).***

Although chronic viral infection can lead to T cell exhaustion, viruses have also been implicated in contributing to autoimmunity through molecular mimicry. Some viral proteins are similar to self antigens and therefore illicit specific immune responses that can cross react with self-antigens. For instance, the EBV protein EBNA-1 cross reacts with the self-antigen Ro, a common target of autoantibodies ***(Toussirot and Roudier, 2008).***

Genes and genetics in SLE:

Genetic predisposition influences the development of SLE in major ways. Although in rare cases this is caused by deficiency of a single gene (e.g. C1q) ***(Moser, 2009)***, it commonly results from the combined effects of a large number of genes. Each allele contributes only mildly (odds ratio ~1.5) and the accumulation of several genes is presumed necessary to significantly increase the risk of SLE. The combinations of risk alleles that lead to predisposition and the mechanisms through which they contribute to autoimmunity are poorly understood. In fact, most single nucleotide polymorphisms (SNPs) associated with SLE fall within noncoding DNA regions and represent markers of co-segregated alleles. Not with standing, most of them are associated with genes presumed to be involved in the immune response.During the past few years, genome-wide analysis have substantially increased the number of candidate genes associated with SLE. Some genes have been associated with several autoimmune diseases (e.g. STAT4 with rheumatoid arthritis; PTPN22 with rheumatoid arthritis and

diabetes), yet others appear to specifically increase the risk of SLE. A recent large-scale replication study confirmed some of the above-mentioned associations and identified TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for SLE. Although promising, the loci identified so far can account only for ~15% of the heritability of SLE. Thus, although the identification of candidate genes and alleles represents an important step in our understanding of the pathogenesis, the relative importance of each gene in the overall disease process and its particular contribution to phenotype and severity remain to be defined ***(Crispín et al., 2010).***

The influence of sex hormones on SLE:

Although men can develop lupus, the disease is much more prevalent in women of childbearing age. It has been shown in murine models that addition of estrogen or prolactin can lead to an autoimmune phenotype with an increase in mature high-affinity autoreactive B cells that can outcompete low-affinity autoreactive B cells ***(Cohen-Solal et al., 2008).***

Although hormones influence SLE development in mice, it has recently been shown that the sex chromosomes themselves influence the expression of SLE. In gonadectomized female and male mice, that have been genetically manipulated to express XX, XO (female), XY or XXY (male), the presence of two X chromosomes increases the severity of SLE disease ***(Smith-Bouvier et al., 2008).***

Although it is clear that hormones can influence autoimmune development in murine models, the use of oral contraceptives does not influence SLE disease flares. Interestingly, a significant number of men suffering from SLE have higher estradiol levels and lower testosterone levels in comparison with healthy individuals ***(Crispín et al., 2010).***

Immunological Abnormalities:

SLE is characterized by immune dysregulation involving both the innate and adaptive immune systems and all effector mechanisms have been shown to be defective. Much of our knowledge about immune dysregulation has been adapted from animal models because immune dysregulation in human SLE is much more difficult to study. Current hypotheses regarding loss of tolerance in SLE suggests that one or more of the following factors play a role: the generation of self-antigens on cell surfaces following apoptosis; abnormalities of innate immunity including Toll-like receptors; abnormalities of all arms of the adaptive immune system including antigen-presenting cells, T cells, and B cells; epigenetics; and, most recently, abnormal regulation of interferon-α ***(Silverman and Eddy, 2011).***

TNF-α participates in the autoimmune process in diverse ways ***(Postal and Appenzeller, 2011).***

Environmental T cell mimics stimulating autoreactive T cells are responsible for the initiation of autoantibodies to SLE-related autoantigens. These T cell responses are restricted by relevant HLA-DR and/or DQ molecules. Normally the generation