Epidemiology of Lupus Nephritis in Egyptian Children

THESIS

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Abstract

Lupus nephritis is A FREQUENT AND SERIOUS COMPLIICAATION IN VIRTUALLY MOST CHILDREN WITH SLE ' RANGING FORM MINIMAL IN VOLVEMENT TO PROGRESSVE RENAL FAILURE BECAUSE OF UN DETECTED IN Cidence of lupus nephritis and its epidemiology Egyptian children, this study included ١٠٠ patients with lupus nephritis following in the rheumatology clinic at Cairo University children hospital and aimed to describe their different clinical , laboratory and pathological presentation , to investigate the clinic pathological correiation and medication received and follow up achieved as well .

KEY WORDS :

Epidemiology ,lupus nephritis , renal biopsy ,

Egyptian children , incidence , statistical value , renal

Presentation , serum creatinine .

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List of abbreviations

ACE	: Angiotensin converting enzyme
ACR	: American college of rheumatology
AI	: Activity index
ANA	: Anti nuclear antibody
Anti-sm	: Anti-smith
aPL	: Antiphospholipid
ARBS	: Angiotensin receptor blockers
CCBS	: Calcium channel Blockers
CI	: Chronicity index
CKD	: Chronic kidney disease
CNS	: Central nervous system
CSF	: Cerebro spinal fluid
CT	: Computerized tomography
DNA	: Deoxyribonucleic acid
DPLN	: Diffuse proliferative lupus nephritis
ds-DNA	: Double stranded DNA
EBV	: Epstein Barr virus
ECG	: Electrocardiograph
EM	: Electron microscopy
ESR	: Erythrocyte sedimentation rate
ESRD	: End stage renal disease
FANA	: Fluorescent antinuclear antibody
GFR	: Glomerular filtration rate
HIV	: Human immunodeficiency virus
HLA	: Human leukocyte antigen
HPF	: High power field
IC	: Immune complex
IF	: Immunofluorescence
Ig	: Immunoglobulin
IV	: Intravenous
IVIG	: Intravenous immunoglobulin
LA	: Lupus anticoagulant
LAI	: Lupus activity index

LE	: Lupus erythematosus
LM	: Light Microscopy
LMN	: Lupus membranous nephropathy
LN	: Lupus nephritis
MCTD	: Mixed connective tissue disease
MRI	: Magnetic resonance imaging
MTX	: Methorexate
NIH	: National institute of health
NPLE	: Neuropsychiatric lupus erythematosus
NSAID	: Non steroidal anti-inflammatory drugs
RBC'S	: Red blood corpuscles
RNP	: Ribonucleoprotein
RTA	: Renal tubular acidosis
SD	: Standard deviation
SLAM	: Systemic lupus activity measure
SLE	: Systemic lupus erythmatosus
SLE-DAI	: SLE-disease activity index
SSA	: Sjogren syndrome A
SSB	: Sjogren syndrome B
TES	: Thrombotic events
UV	: Ultraviolet
WBC'S	: White blood corpuscles
WHO	: World health organization

Introduction and aim of work

Introduction:

Renal disease in systemic lupus erythematosus is a major clinical problem, responsible for significant morbidity and mortality **(*Herrare, ١٩٩٩*).** The rate of organ involvement is higher in the child compared with the adult's lupus patients with clinical symptoms of renal involvement occurring in ٣٠% -٧٠% of patients **(*Niaudet, ٢٠٠٠*)**.

Clinical presentation varies from asymptomatic urinary abnormalities to acute nephrotic and/or nephritic syndrome ***(Lim et al., ١٩٩٩).*** The exact incidence of renal disease in SLE patient is unknown and it is important to recognize that the spectra and severity of renal disease vary considerably from one patient to another which has both prognostic and therapeutic implications **(*Schur, ١٩٩٢*).**

The prognosis for patient with SLE has improved dramatically but in patient with lupus nephritis the prognosis continues to be guarded despite treatment and many patients progress to chronic renal failure ***(McCurdy et al., ١٩٩٢*)**.

Aim of work:

The aim of this work is to trace the incidence of lupus nephritis among Egyptian children regarding their number with different clinical, laboratory and pathological presentation, medication received and follow up achieved as well.

Systemic Lupus Erythematosus

Introduction:

Systemic lupus erythematosus is an episodic multisystem disease characterized by wide spread inflammation of the blood vessels and connective tissue, it is regarded as a prototype of autoimmune disease in humans on a background of a genetic predisposition of the disease **(*Cassidy and petty, ١٩٩٠*)**.

This disease occurs primarily in young women and ranges in severity from a mild disease with rash and arthritis to a devastating illness with renal failure and profound nervous system disturbance **(*Pisetsky et al., ١٩٩٧*).** Within the past three decades, as treatment modalities have improved life expectancy of children diagnosed with SLE, a new concept of irreversible organ damage has provided a better understanding of lupus as a chronic disease **(*Pongmartufani et al., ٢٠٠٦*).**

***Epidemiology of SLE*:**

- Incidence & prevalence:

According to lupus foundation, approximately ١.٥ million people, mostly women of reproductive age have been diagnosed with SLE **(*Emre et al., ٢٠٠١*).** The incidence varies with age, race, sex **(*Sibgsen, ١٩٩٠*),** the overall age standardized one-year period prevalence rate as estimated by a recent study of a geographically complete cohort from Nottingham is at ٢٤.٧ per ١٠٠.٠٠٠ **(*Hopkinson et al., ١٩٩٤*).**

Data from pediatric rheumatic disease registries confirm that SLE accounts for less than ١ percent of patients in pediatric rheumatology clinics in the United Kingdom ***(Symmon et al., ١٩٩٤*).**

- Age onset:

١٥-٢٠ % of SLE patients were diagnosed for the first time during childhood **(*Emre et al., ٢٠٠١*).**The peak childhood onset between ١١and ١٥ years of age, rarely does it affect children below the age of ٥ **(*Pongmaritani, ٢٠٠٠*).**

- Sex ratio:

SLE occurs ١٠ times more commonly in women than in men, the overall prevalence of SLE in women in approximately ١٠٠ per ١٠٠.٠٠٠ **(*McCarty et al., ١٩٩٩*).** There are approximately ٣ million women and ٣٠٠.٠٠٠ man affected worldwide. In one study involving Turkish children, the ratio of female to male children affected with SLE was ٩,٨ : ١ which is much higher than ٤,٥ : ١ ratio found in other pediatric studies **(*Emre et al., ٢٠٠١*).**

- Race and geography:

Rates of SLE were found to be highest in African American females and lowest in white males **(*McCarty, ١٩٩٥*)** and studies suggest them African American and Hispanic children have a higher incidence of SLE.

Black children have a greater prevalence for more severe renal and neuropsy-chiatric disease, more discoid rash and increased prevalence of cardiac disease as a result of complication of **SLE (Stichwel, Arce & *Pascual, ٢٠٠٤).***

Pathophysiology:

- Genetics:

Epidemiology data on the familial aggregation, sibling ratio and the disease concordance rate in twins all support a genetic component **(*Priori et al., ٢٠٠٣*).**

The prevalence of SLE is estimated to be ٢.٦ to ٣.٥ % in the first degree relatives of SLE and the risk of developing the disease in sibling is ١٠-٤٠

times higher than that in the general population the concordance rate in monozygotic twins (٢٤ to ٥٦ %) compared to dizygotic twins (٢ to ٥ %) (Jarvinen et al,١٩٩٢). Several case control studies have identified several genes, providing highly convincing evidence for allelic association with SLE **(*Gaffrey et al., ٢٠٠٠*).** Eight loci that best support SLE susceptibility have been identified this far including ١q٢٣, ١q٢٥-٣١, ١q٤١-٤٢ (located on chromosome ١) ٢q٣٥-٣٧ (Located on chromosome ٢) ٤p١٦-١٥.٢(Located on chromosome ٤), ٦p١١-٢١ (Located on chromosome ٦), ١٢p٢٤ (Located on chromosome ١٢) and ١٦q١٢ (Located on chromosome ١٦) (Koskenmies et al., ٢٠٠٤). All eight of these loci have been confirmed in at least one independent cohort for linkage to SLE. Locus ١٦q١٢ is linked to both SLE and other at autoimmune disease suggesting an interaction with other susceptibility loci which manifest multiple autoimmune diseases **(*Cantor et al., ٢٠٠٤*).**

- Immunological abnormalities:

SLE is an immune complex (IC)-associated systemic autoimmune disease. The production of abnormal antibodies by polyclonal B cell is the hallmark sign of this disease **(*Kammer, ٢٠٠٢*).** In people with a predisposition for SLE, cellular antigens exposed during apoptosis may incite the immune response (Pongmarutani et al., ٢٠٠٦). The initiation of the immune response is characterized by the presence of activated helper T cell that induce a B cell response, leading to hyperglobulinemia, the secretion of pathogenic autoantibodies (antidouble stranded DNA antibody and anti-smith) and the formation of immune complex.

The T cells are inable to suppres the B cell clones because of T cell deregulation, resulting in excess CD٤, T cell activity and deficient CD٨, cytotoxic suppressors function (Kammer, ٢٠٠٢). Additionally B and T cell interaction is facilitated by several cytotoxines (interleukin -١٠) and co-

stimulatory molecules (CD٤٠/CD٤٠L,B٧/CD٢٨/CTLA-٤) which initiate the interactions along with the body's impaired phagocytic clearance of IC perpetuate the immune response that lead to tissue injury ***(Mok & Lau*** **,** ٢٠٠٣**) .**

- Complement deficiency:

While the activation of complement is involved in tissue damage, inherited deficiencies of components of the classic pathway are strongly associated with the development of SLE. Lupus develops in many patients with complete deficiencies in C١q (٩٠%) &C٤ (٧٥%), suggesting that these molecules have a protective role against the development of the disease **(*Pickeriny Mc et al.,*** ٢٠٠٠**).** The protective role of C١q has been confirmed by the observation of severe lupus nephritis in C١q deficient mice.

- Hormonal factors:

Females are affected at least five to nine times more frequently than males which suggest an estrogen-mediated immune hyperactivity, it has been noted the activity of SLE is increased in the ٢ weeks preceding menstruation **(*Cassidy &Petty,*** ١٩٩٠**),** during which the level of estrogen is increased. The use of oral contraceptives with high level of estrogen were reportedly associated with the lupus activity but more recent reports in which the estrogen dose was much lower failed to show a relationship with the disease activity **(*Julkumen,*** ١٩٩١**).**

- Environmental Factors:

✧ **Ultraviolet B irradiation:**

Ultraviolet B result in photooxidation and degradation of native DNA in the skin, thereby increasing its Immunogenicess **(*Casciola, Rosen,*** ١٩٩٧**).** Exposure of skin to UV lights results in movement of Ro (SS.A), La (SS-B) and U١RNP antigens to the surface of keratinocytes where they

might be bound by sensitized T cells or antibodies resulting in a flare of lupus dermatitis (***Than, ٢٠٠١).***

✧**Infection:**

Infection have been postulated to play a role in the initiation of the disease, the pathogen which have been extensively studied include Epstein Barr virus EBV, Cytomegalovirus and parvovirus B-١٩ (***Cooper et at.; Hayashi et al., ١٩٩٨).*** Enzyme linked immunosorbent assay test have been used to link EBV as an environmental trigger (***James, Harley and Scofield, ٢٠٠١),*** to large cohort and found that those with SLE were positive as compared to matched control group.

Eleven percent of SLE patient showed evidence of infection with hepatitis C virus compared to ١% of matched control using third generation recombinant immoblot assay and PCR (***Ramos Casal et at., ٢٠٠٠).*** Case studies involving cytomegalovirus and parvovirus B-١٩ and SLE have increased interest in both of these viruses and their relationship to SLE (***Diaz et al., ٢٠٠٢).***

✧**Drugs and chemicals:**

Several drugs particularly those metabolized by a acetylation in the liver, such as procaninamide or hydralazine, can induce a lupus like syndrome ***(Fritzele, ١٩٩٤)***. Other drugs as penicillamine, Isoniazid, interferon-alpha methyldopa, chlorpromazine and diltiazem are all likely causes of lupus like syndrome.

Anticonvulsants (e.g phenytoin, mephenytion, trimethadone, ethosuximide) quinidine, antithyroid drugs and antimicrobial agents (e.g. sulfonamides, rifampcin) may possibly induce lupus (***Grant, ١٩٩٠)***. Clinical manifestations associated with the drug-induced lupus include fever, cutaneous rash, arthralgia and serositis, whereas renal, hematological or neurological symptoms are rare.