EVALUATION OF THYROID FUNCTIONS IN JUVENILE RHEUMATOID ARTHRITIS

Thesis
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My greatest father

My lovely mother

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مَالَمْ يَعْلَمْ ﴿٥﴾

صدق الله العظيم

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LIST OF ABBREVIATIONS

ACR	: American collegue of rheumatology
ADCC	: Antidestructive cytotoxic cell
AITD	: Autoimmune thyroid disease
AMA	: Antimicrosomal antibodies
ANA	: Antinuclear antibody
APC	: Apoptotic cell
ATA	: Antithyroid antibody
ATg	: Antithyroglobulin antibodies
CBC	: Complete blood count
CLT	: Chronic lymphocytic thyroiditis
COX2	: Cyclooxygenase II inhibitors
DMARDS	: Disease modifying antirheumatic drugs
DXA	: Dual energy radiograph absorptiometry
EoPA	: Early onset pauciarticular
ESR	: Erythrocyte sedimentation rate
FDA	: Food and drug administration
GD	: Graves' disease
HLA	: Human leucocyte antigen
HT	: Hashimoto's disease
IFNγ	: Interferon gamma
IL_4	: interleukin 4
IL-I	: Interleukin I
IM	: Intramuscular
IVIG	: Intravenous immunoglobulins
JCA	: Juvenile chronic arthritis
JIA	: Juvenile idiopathic arthritis
JRA	: Juvenile rheumatoid arthritis

LDL	: Low density lipoprotein
MAS	: Macrophage activation syndrome
MCH	: Major histocompatiblity complex
MTX	: Methotrexate
NSAIDS	: Non steroidal anti-inflammatory drugs
NTG	: Non toxic nodular goiter
PO	: Per oral
PTU	: Propyl thiouracil
qid	: Four time daily
RA	: Rheumatoid arthritis
RF	: Rheumatoid factor
SD	: Standard deviation
SDS	: Standard deviation score
SLE	: Systemic lupus erythematosus
SS	: Systemic sclerosis
T3	: Trioidothyronine
T4	: Thyroxine
Tg	: Thyroglobulin
TgAb	: Antithyroglobulin antibodies
Th	: T helper cell
tid	: Twice a day
TNF-α	: Tumour necrosis factor alpha
TPO	: Thyroperioxidase
TPoAb	: Antithyroid perioxidase antibodies
TSH	: Thyrotropin stimulating hormone
TSHR	: thyrotropin receptor
TSRAb	: Thyrotropin receptor antibody

INTRODUCTION AND AIM OF THE WORK

The association between autoimmune rheumatological and thyroid disorders has long been known, the most common being is the association of rheumatoid arthritis and autoimmune thryoiditis. It has been well established that antithyroglobulin antibodies (ATg) and antimicrosomal antibodies (AMA) may be present in various thyroid disorders and other systemic autoimmune diseases ***(Ozgen et al., 2001)***. Rheumatoid arthritis (RA) may confer an autoimmune locus for earlier development of hypothyroidism and the prevalence may be generally higher than that in the normal population ***(Chan et al., 2001)***.

This study is aimed to evaluate thyroid hormones and autoantibodies among patients with juvenile rheumatoid arthritis in order to diagnose cases with autoimmune thyroiditis and/or subclinical hypothyroidism in relation to the type of onset and severity of arthritis.

JUVENILE RHEUMATOID ARTHRITIS (JRA)

Juvenile rheumatoid arthritis (JRA) is a chronic arthritis of childhood which comprises several different subgroups. It is one of the most common rheumatic diseases of childhood. Because the majority of children are rheumatoid factor negative, it is also known as juvenile idiopathic arthritis (JIA) or juvenile chronic arthritis (JCA) ***(Cassidy & Petty, 2001)***.

Epidemiology

The incidence of JRA is approximately 13.9/100.000/ year among children aged 16 years or younger ***(Miller and Cassidy, 2004)***. ***El Gamal et al. (1999)*** reported that the incidence of JRA in relation to outpatient clienteles in the Children's Hospital Ain Shams University during the year 1994 was 9.8/100.000 children.

Neither the etiology nor risk factors of JRA have been identified. It is considered to be an autoimmune disease. The presence of chronic synovitis, T-cell abnormalities, abnormal immunoregulation and cytokine production, autoantibodies, immune complexes, and complement activation suggests that cell mediated and/or humoral processes are involved. Infection may have a possible role ***(Ruddy et al., 2001)***.

JRA is classified as systemic, pauciarticular (oligoarticular), or polyarticular disease according to onset within the first 6 months. Pauciarticular and polyarticular JRA tend to affect girls more often than boys. Systemic-onset disease occurs with equal frequency in boys and girls.

Pauciarticular JRA tends to affect children in early childhood. Systemic-onset disease can also occur in early childhood; however, it is sometimes observed in late childhood or early adolescence. Polyarticular JRA can occur throughout childhood and adolescence. Rheumatoid factor-positive disease, similar to rheumatoid arthritis in adults, is more often found in adolescents ***(Cassidy and Petty, 2001)***.

Genetic susceptibility

The most extensively studied susceptibility locus for autoimmune disorders is the major histocompatibility complex (MHC) located on chromosome 6p. The class I gene HLA-B27 has consistently been found to pose risk for pauciarticular JRA especially among older males. HLA-DR_1, and DR_4, class II genes, have been reported to increase the risk for polyarticular JRA. HLA-DR_4 is associated with RF-positive polyarticular disease in older children but this gene might be protective in patients with early onset pauciarticular arthritis (EOPA) ***(Prahalad et al., 2000)***.

Among children who carry HLA-A2 and any two HLA-DR alleles (HLA-DR_3,-DR_5, DR_6, DR_8), the median age at onset of pauciarticular disease was only 2.5 years ***(Murray et al., 1999)***.

Pathological features

The articular pathology of JRA shares features in common with RA. Synovial biopsy specimens reveal villous hypertrophy and hyperplasia of the synovial lining. Cellular infiltration, predominantly with T lymphocytes, occurs early in

the disease (figure 1). The inflammatory process eventually results in progressive erosion and destruction of articular cartilage. Joint destruction is thought to occur later in the course of JRA than in adult disease ***(Wedderburn and Woo, 1999)***. The greater thickness of the juvenile articular cartilage could account for this difference.

Both RA and JRA are believed to be mediated by the Type 1 T helper (Th1) phenotype of lymphocytes ***(Cassidy and Petty, 2001)***. ***Wedderburn and Woo***, ***(1999)*** have shown that there was a very high number of IFN-γ producing cells, both in the CD4 and CD8 populations. More recently, ***Scola et al. (2002)*** have demonstrated similar cytokine findings in the more-difficult-to-obtain JIA synovial tissue. Cytokines that are involved in the inflammatory process are also similar, including TNF-α and IL-1, enabling control of these responses by the use of appropriate, biologic disease-modifying agents. However, at least in the case of pauciarticular JRA, Th2-mediated inflammatory responses may have a role to play. ***Murray et al***. ***(1998)*** showed that synovial fluid from patients with pauciarticular disease significantly overexpresses IL-4 messenger RNA relative to synovial fluid from patients with polyarticular JRA and RA. ***Thompson et al***. ***(2001)*** documented CCR4-bearing CD4 synovial fluid lymphocytes with a phenotype that was Th2-like in that they produced greater IL-4 than IFN-γ. ***Raziuddin et al***. ***(1998)*** found a distinctly enhanced mixed-Th1/Th2-cell-response cytokine pattern in patients with systemic JRA.

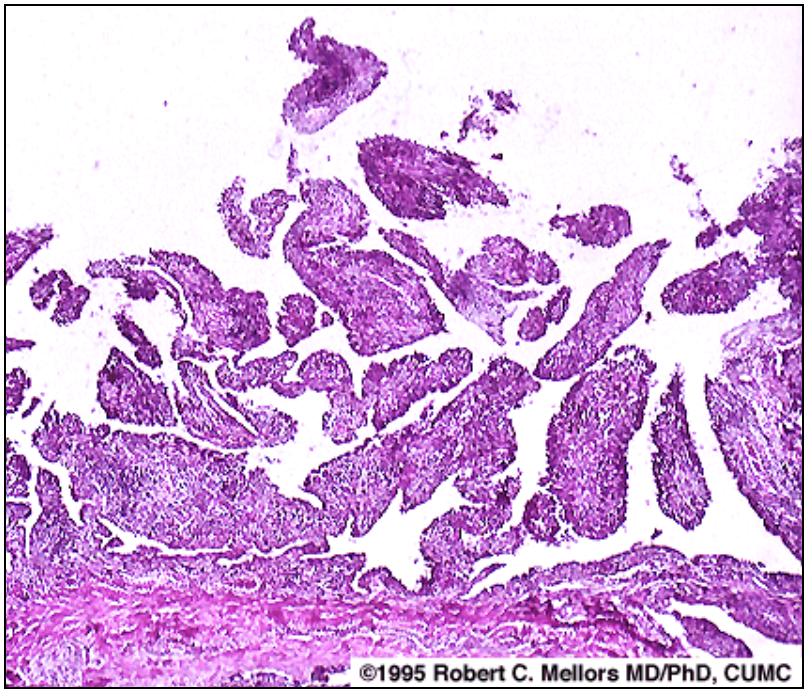

Figure (1): Chronic proliferative and exudative synovitis (of knee) in juvenile rheumatoid arthritis. H&E.

(Quoted from Mellors, 1995)

Diagnosis

A detailed physical examination is a critical tool in diagnosing JRA. Physical findings are important to provide criteria for diagnosis and to detect abnormalities suggestive of other possible diagnoses. The diagnosis of JRA is based on the physical finding of arthritis (or synovitis) in at least one joint that persists for at least 6 weeks, with other causes being excluded and with onset when the individual is younger than 16 years according to American Collegue of Rheumatology (ACR). Arthritis on examination is defined as either joint swelling (although trauma can also cause swelling and may