# Screening of Growth Impairment inJuvenile Rheumatoid Arthritis, Systemic LupusErythematosus and Autoimmune Chronic Liver Disorders In Childhood

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aCL: Anti-cardiolipin

Anti-LKM1: Anti-liver-kidneytype 1

Anti-neutrophil cytoplasmic antibodies ANCA:

aPL: antiphospholipid

ACR:American College of Rheumatology

ACLD: Autoimmune chronic liver disorders

AD: Autoimmune disease

AIH: Autoimmune hepatitis

APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

AIRE: Autoimmune regulator gene

ASC: Autoimmune sclerosing cholangitis

aSLE: Adult SLE

ANA: Anti-nuclear antibodies

Anti ds DNA Ab: Anti-double strand DNA antibodies

Anti sm Ab: Anti-smooth muscle antibodies

ALT: Alanine transaminase

ASGP-R: Anti-asialoglycoprotein receptor antibodies

AST: Aspartate transaminase

ASC: Autoimmune sclerosing cholangitis

BMI: Body mass index

CD: Celiac disease

CBC: Complete blood count

cSLE: Childhood-onset SLE

CLD: Chronic liver diseases

CT: Computerized axial tomography

CRP: C-reactive protein

CYP2D6: Cytochrome P4502D6

DM 1: Diabetes mellitus type 1

DLE: Discoid lupus erythematosus

ELISA: Enzyme-linked immunosorbant assay

ERA: Enthesitis-related arthritis

ESR: Erythrocyte sedimentation rate

EULAR: European League Against Rheumatism

ENA: Extractable nuclear antigen

GGT: Gamma glutamyltransferase

GLADEL: Grupo Latino Americano de Estudio Del Lupus

HV: Height velocity

HLA: Human leukocyte antigen

HLH: Hemophagocytic lymphohistiocytosis

IBD: Inflammatory bowel disease

ITP:Idiopathic thrombocytopenic purpura

Ig: immunoglobulin

IAIHG: International Autoimmune Hepatitis Group

ILAR:International League of Associations for Rheumatology

IL: Interleukin

JAIH: Juvenile AIH

JIA: Juvenile idiopathic arthritis

JPsA:Juvenile psoriatic arthritis

JRA:Juvenilerheumatoid arthritis

LC1: anti-liver cytosol antibodies type 1

LBW: Low birth weight

LDL: Low density lipoprotein

LAC: Lupus anticoagulant

LN: Lupus nephritis

LUMINA: Lupus in Minorities

Lyp: Lymphocyte phosphatase

MRCP: Magnetic resonance cholangiopancreatography

MRI: Magnetic resonance imaging

MAS: macrophage activation syndrome

MHC: Major Histocompatibility Complex

NK: natural killer

NPSLE: Neuropsychiatric involvement with SLE

pANCA: Perinuclear antineutrophil cytoplasmic antibodies

PHV: Peakheight velocity

PD: Power Doppler

PSC: Primary sclerosing cholangitis

PUO: Pyrexia of unknown origin

PTPN22:Protein tyrosine phosphatase non-receptor 22

RANKL: receptor activation of nuclear factor-k B ligand

RA:Rheumatoid arthritis

RF: rheumatoid factor

RNP: Anti-ribonucleoprotein

SAA: Serum amyloid A

SJIA: Systemic JIA

SLA: anti-soluble liver antigen antibodies

SLE: Systemic lupus erythematosus

SD: Standard deviations

SDI: SLE damage index

SNP: Single nucleotide polymorphism

Sm: Anti-Smith

Th1cells: T Helper 1 cells

Th 2 cells: T Helper 2 cells

Treg: T-regulatory

TNF-α:Tumor necrosis factor-alpha

US: Ultrasound

# ABSTRACT


## Screening of growth impairment in juvenile rheumatoid arthritis, systemic lupus erythematosus and autoimmune chronic liver disorders

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**Introduction:** Autoimmune diseases are associated with growth impairment. This may be a consequence the inflammation with disease activity and is caused by the high-dose corticosteroids treatment.

**Aim:** Screening of growth impairment in juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE) and autoimmune chronic liver disorders (ACLD).

**Methods:** 1000 cases of school children and adolescents (both sexes) of JRA, SLE and ACLD. The study will be conducted in the 4 main pediatric hospitals in Alexandria, to detect growth impairment and delayed puberty in these group children and adolescents using axiological parameters and Tanner staging from June 2010 to August 2015.

**Results**: In JRA group of school age children (both sexes) in 3rd - <10th height percentile, the percentage of males and females were 51.7 and 46.5 respectively. Pubertal assessment (Tanner staging) of the studied SLE group of school age male children and adolescents shows that 48% of cases were in the Tanner stage 1 category which means delayed puberty was in a large number of cases.

**Conclusions:** JRA, SLE and ACLD are associated with growth impairment and delayed puberty.



**Keywords:** growth impairment, delayed puberty, short stature, under-weight.



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# INTRODUCTION

Autoimmune diseases are a group of diseases in which the body produces antibodies against its own tissue not against infective agents. It is characterized by severe inflammation and widespread tissue damage **(Eaton et al., 2007).** Autoimmune diseases occur when there is interruption of the usual control process thereby, allowing the system to malfunction and attack healthy cells and tissues. A common example of autoimmune disease is Type I Diabetes (DM 1) which affects nearly a million people in the United States. Some other common autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus (SLE) and vasculitis **(Reeves et al., 2009).**

Autoimmune responses emerge following infection by a pathogen, whose protein(s) hold structural similarities to regions on proteins of the host. Thus, antibodies evoked against a pathogen might cross-react with a self-protein and act as auto-antibodies, and the concerned auto-antigen then provides a source for persistent stimulation.The onset of autoimmune disease is associated with a trigger which can be pulled in numerous ways. In one possible example, certain substance in the body that is normally confined to a specific area may be released into another area due to internal trauma; the translocation may stimulate the immune system to recognize a natural body component as foreign and trigger an autoimmune response. In another example, a normal component of the body may be altered via virus, a drug, sunlight or radiation; the altered substance may then appear foreign to the immune system **(Ray et al., 2012).** Very rarely, a foreign substance resembling a natural body component may enter the body thereby, inducing the immune system to target both the similar body substance and the foreign substance. Just as the triggers for autoimmune disorders are wide and varied, so are their effects. The debilitating effects of various autoimmune disorders include the destruction of a specific type of cell or tissue, stimulation into excessive growth, or interference in function.

Organs and tissues affected by more common autoimmune disorders include components of the endocrine system, such as thyroid, pancreas and adrenal glands; components of the blood such as red

blood cells; and the connective tissues, skin, muscles, and joints **(Ray et al., 2012).**

Autoimmune diseases in children include juvenile rheumatoid arthritis (JRA), systemic lupus erythematosus (SLE) autoimmune chronic liver disorders among many others **(Rose and Mackay, 2007).**

Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA), is the most common form of arthritis in children and adolescents **(Hussein, Emara and Mohamed, 2015).**

Juvenile systemic lupus erythematosus a multi-system disorder that is characterized by widespread immune deregulation, formation of autoantibodies and immune complexes, resulting in inflammation and potential damage to a variety of organs. It is not uncommon for children to present with non-specific symptoms **(Thabet et al., 2014).**

Autoimmune liver disorders are inflammatory liver diseases characterized histologically by a dense mononuclear cell infiltrate, including plasma cells, in the portal tract and serologically by the presence of non-organ and liver-specific autoantibodies and increased levels of Immunoglobulin G (IgG), in the absence of a known etiology. They usually respond to immunosuppressive treatment, which should be instituted as soon as diagnosis is made. The onset of these conditions is often ill-defined, frequently mimicking acute hepatitis. There are two liver disorders in which liver damage is likely to arise from an autoimmune attack: autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC) **(Mieli-Vergani G and Vergani D, 2013).**

Many autoimmune diseases are chronic illness which may lead to growth impairment either because of illness itself or because of treatment required for it. Short statue is commonly perceived to be associated with social or psychological disadvantage **(Voss, 2001).**

Juvenile idiopathic arthritis is characterized by chronic inflammation in various tissues of the body, and can affect joints, ligaments, muscles and internal organs. Over the long term, inflammation can cause stiffening and deformation of the affected joints, and can lead to significant growth impairment. Growth impairment is significantly more severe in children with the systemic subtype of the disease and in children in whom many joints are affected. Growth impairment is also more severe in children with extensive joint damage than in children with early or moderate anatomical changes.

Factors responsible for growth impairment in chronically ill children include frequent infections, primary and secondary malnutrition, long-term stress related to being chronically ill or and side effects of therapy. It is often difficult to tell how much growth impairment can be attributed to the disease itself, and how much to the side effects of treatment (**Umlawska and Prusek-Dudkiewicz, 2010).**

Growth impairment in children with JIA is especially severe when autoimmunological activity has been elevated over a long period, which is associated with high levels of the pro-inflammatory cytokines

IL-1, IL-6 and TNF-α. Growth impairment in children with JIA is especially severe when autoimmunological activity has been elevated over a long period, which is associated with high levels of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α **(Martensson, Chrysis and Savendahl, 2004).** These cytokines reduce secretion of growth hormone from the pituitary gland, and also act directly on the growth plates of the long bones Inflammation also inhibits blood circulation in the affected joints which limits the supply of oxygen and nutrients to the growth plates of the long bones. At first, there is an increase in the rate of bone formation in the vicinity of the affected joint. However, if auto-immunological activity persists for a long time, cell proliferation in the growth plates ceases before development is complete, and the length of the limbs is likely to be irreversibly affected. Effective and timely treatment can preserve growth potential in children with JIA, thereby allowing bone growth to catch up. The long term use of corticosteroids in

JIA has been associated with growth retardation, but growth can also slow down without steroid treatment **(Philpott, Houghton and Luke, 2010).**

Short stature frequently occurs in children suffering from juvenile idiopathic arthritis. The potential of disturbance of linear growth is greater in children with systemic or non-systemic polyarticular disease of long duration **(Bechtold et al., 2004).**