



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



MONA MAGHRABY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



MONA MAGHRABY



Growth Pattern in Juvenile Idiopathic Arthritis in Relation to Insulin Growth Factor-1 and S100A8/9 Protein.

Thesis proposal Submitted for partial fulfillment of PhD in childhood studies

(Child Health and Nutrition)

Medical Studies Department for children

By

Ahmed Mahmoud Zaki Mohamed

M.Sc Pediatrics- Cairo University

Assistant Researcher- National Research Centre

Under Supervision of

Prof. Hayam Kamal Nazif

Professor of Pediatrics

Department of Medical Studies for children

Prof. Moushira Erfan Zaki

Professor of Human Genetics , Biological Anthropology

Department , Medical Research Division , National Research Centre

Prof. Naglaa Kholoussi

Professor of Clinical Pathology

Department of Clinical Pathology

National Research Centre

Faculty of Postgraduate Childhood Studies

Ain Shams University

2021

Abstract

juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease which affect growth before age of 16 years. The growth hormone (GH)/insulin-like factor-1 (IGF- 1) axis is a main regulator of linear growth, and the major part of circulating IGF-1 levels is liver derived. S100 calcium-binding proteins are associated with acute / chronic inflammatory disorders. The most familiar of S100 proteins is S100A8/A9 (calprotectin). The aim of our study was to evaluate the physical growth pattern in children with JIA. To measure the level of serum IGF-1 and to compare it with healthy controls subjects and also to assess serum S100 A 8/9 protein and its relation to growth pattern and IGF-1.

The study was a case control study which included 40 patients of both sexes with (JIA), their ages will range from 6-10 years. *All patients and controls were subjected to the following:-* Growth Assessment and measure serum (IGF-1) level and S100 A8/9 protein.

There was statistically significant difference between Cases and Controls regarding height-for-age z-score (HAZ), 37.5% of cases were short stature were 10% in controls. There was statistically significant decrease in Weight and BMI among Cases versus Controls. Percentage of underweight of cases were higher among cases versus controls. There was statistically significant decrease in serum Insulin-like growth factor 1 among Cases versus Controls. There was statistically significant increase in S100A8/9 Protein among Cases than Controls. There were statistically significant positive correlation between IGF-1 and height



إِنْ أُرِيدُ إِلَّا الْإِصْلَاحَ مَا اسْتَطَعْتُ وَمَا تَوْفِيقِي إِلَّا
بِاللَّهِ عَلَيْهِ تَوَكَّلْتُ وَإِلَيْهِ أُنِيبُ

صدق الله العظيم



ACKNOWLEDGEMENTS

First and foremost, all praise and all thanks to **ALLAH**, who has guided and enabled me by his mercy to fulfill this thesis which I hope to be beneficial for all.

I would like to express my profound gratitude to *Prof. Dr. Hayam Kamal Nazif*, Professor of Pediatrics Department of Medical Studies for children for her most valuable advises and support all through the whole work and for dedicating much of her precious time to accomplish this work.

I am also grateful to *Prof. Dr. Moushira Erfan Zaki* Professor of Human Genetics , Biological Anthropology Department, Medical Research Division , National Research Centre for her unique effort, considerable help, assistance and knowledge she effored me throughout the performance of this work.

My special thanks to *Prof. Dr. Naglaa Kholoussi*, Professor of Clinical Pathology, Department of Clinical Pathology, National Research Centre for her kind care and great assistance throughout the work.

My special thanks to: Nermin Hassan El gharbawy , Lecturer of Physical Medicine, Rheumatology and Rehabilitation Faculty of Medicine, Ain Shams university. Assem Metwally Abo-Shanab , Immunogenetics department, National Research Centre. Sanaa kamal Mohamed, Professor biological anthropology. Ramy El-Sherbini ,Researcher and lecturer of pediatric and neonatology Biological anthropology department National research centre.

My special thanks to all staff members in Faculty of Postgraduate Childhood Studies Ain Shams Universityfor their cooperation in this work.

My deepest gratitude I extend to my whole family who offered me support, advise and motivation.

Ahmed Mahmoud Zaki Mohamed

List of Contents

Items	Page. No.
List of Contents	I
List of Abbreviations	
List Of Tables	
List Of Figures	
Introduction	
Aim Of The Work	
Review Of Literature	
Chapter 1 Juvenile Idiopathic Arthritis	
Chapter 2 Growth of children with juvenile idiopathic arthritis	
Chapter 3 S100A8/9 protein	
Chapter 4 Insulin-Like Growth Factor-1	
Patient And Method	
Results	
Discussion	
Summary	
Conclusion	
Recommendations	
References	
Arabic Summary	١

List of Abbreviations

AA	arachidonic acid
ACR	American College of Rheumatology
AD	Alzheimer's disease
AEs	adverse events
ANA	antinuclear antibodies
APP	amyloid precursor protein
AS	ankylosing spondylitis
Aβ	amyloid- β
CALP	Calprotectin or (S100A8/9)
CBC	Complete blood count
cJADAS	clinical JADAS
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
CRP	C-reactive protein
CVDs	cardiovascular diseases
DCE-MRI	Dynamic contrast-enhanced MRI
DMARDs	disease-modifying antirheumatic drugs
EIF4EBP1	eukaryotic translation initiation factor 4E-binding protein 1
ELISA	enzyme-linked immunosorbent assay
EPOCA	EPidemiology, treatment and Outcome of Childhood Arthritis
ERA	Enthesitis-related arthritis
FDA	Food and Drug Administration
FOXO	Forkhead Box O
GH	growth hormone
HAZ	height-for-age z-score
HLA	human leukocyte antigen
HRP	Horseradish Peroxidase
HRQoL	health-related quality of life
IAC	Intra-articular corticosteroid
IAV	Influenza A virus
IBD	inflammatory bowel disease
IGF	insulin-like growth factors
IGF1	Insulin-like growth factor 1

IGF-1	insulin growth factor-1
IgM	immunoglobulin
ILAR	International league of Association for Rheumatology
JADAS	Juvenile Arthritis Disease Activity Score
JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JCA	juvenile chronic arthritis
JIA	Juvenile Idiopathic Arthritis
JNK	Jun N-terminal kinase
JPsa	juvenile psoriatic arthritis
JRA	juvenile rheumatoid arthritis
LPS	Lipopolysaccharide
MAS	macrophage activation syndrome
MMP-3	matrix metalloproteinase-3
MRI	magnetic resonance imaging
MRP	myeloid-related protein
MSU	Monosodium urate
MTX	Methotrexate
NO	nitric oxide
N-S	non significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
OD	optical density
PDR	proliferative diabetic retinopathy
PGA	physician's global assessment of disease activity
PMN	polymorphonuclear
PPGA	parent's/patient's assessment of child's well-being
PRCOs	patient-reported or parent-reported outcomes
RF	Rheumatoid factor
rhIGF-1	recombinant human IGF-1
ROS	reactive oxygen species
S	significant
S6K1	S6 kinase 1
SAEs	serious adverse events
sCD163	soluble CD163
SD	Standard deviation
SDS	standard deviation score
sIL-2Rα	serum levels of soluble interleukin-2 receptor α
SLE	systemic lupus erythematosus
SPSS	Statistical Package for Social Sciences

TH	Triamcinolone hexacetonide
TLR	toll-like receptor
TLRs	toll-like receptors
TNF	IL-1 or tumor necrosis factor
VAS	visual analog scale
WAZ	weight-for-age z-score
X2	Chi square test

List of Tables

Table No.	Review of Literature	Page
Table (1)	International League of Associations for Rheumatology (ILAR) classification criteria for chronic arthritis in childhood	7
Table (2)	New classification criteria of macrophage activation syndrome	9
Table (3)	Differential diagnosis of systemic juvenile idiopathic arthritis	13
Results		
Table (1)	Comparison between Cases and Controls regarding demographic data	86
Table (2)	Family history among cases group	86
Table (3)	Frequency of various Clinical manifestations among cases group	86
Table (4)	Comparison between Cases and Controls regarding anthropometric measurements	87
Table (5)	Comparison between Cases and Controls regarding BMI categories	88
Table (6)	Comparison between Cases and Controls regarding height-for-age z-score (HAZ)	89
Table (7)	Comparison between Cases and Controls regarding weight-for-age z-score (WAZ)	89
Table (8)	Comparison between Cases and Controls regarding BMI Z score	90
Table (9)	Comparison between Cases and Controls regarding Complete blood count	91
Table (10)	Comparison between Cases and Controls regarding anemia	91
Table (11)	Comparison between Cases and Controls regarding ESR (mm/hr)	92
Table (12)	Comparison between Cases and Controls regarding hs-CRP (mg/L)	93
Table (13)	Comparison between Cases and Controls regarding S100A8/9 Protein (ng/ml)	94
Table (14)	Comparison between Cases and Controls regarding IGF-1 ng/ml	95
Table (15)	Correlation between IGF-1 ng/ml and other variable	96

Table (16)	Correlation between S100 A8/9 Protein and other variable	99
Table (17)	S100A8/9 Protein (ng/ml) in detection of cases	101
Table (18)	IGF-1 (ng/ml) in detection of cases	102
Table (19)	Correlation between sex and S100 A8/9 Protein	102
Table (20)	Correlation between sex and IGF-1 ng/ml	103
Table (21)	Comparison between males and females regarding anthropometric measurements	103
Table (22)	Comparison between males and females regarding height-for-age z-score (HAZ)	103
Table (23)	Comparison between males and females regarding weight-for-age z-score (WAZ)	104
Table (24)	Comparison between males and females regarding BMI Z score	104

List of Figures

Fig. No.	Review of Literature	Page
Fig.(1)	Salmon-macular rash in systemic juvenile idiopathic arthritis	8
Fig.(2)	Arthritis of the right knee in a child with oligoarticular juvenile idiopathic arthritis	11
Fig.(3)	T1-weighted magnetic resonance imaging of left sacroiliitis in a patient with enthesitis-related arthritis	16
Fig.(4)	The binding of S100A8/A9 to toll-like receptor (TLR) 4 triggers the MyD88-dependent pathway, appearing to play a vital role in inflammation	52
Fig.(5)	IGF-1 downstream effects on transcription, protein synthesis and cell growth	64
Fig.(6)	IGF-1 mechanisms of inhibiting apoptosis	65
Fig.(7)	Pre- and post-synaptic markers influenced by IGF-1	67
Fig.(8)	Showing sample dilution of IGF-1	74
Fig.(9)	Showing sample dilution of CALP	78
Results		
Fig.(1)	Comparison between Cases and Controls regarding Weight (kg), Height (cm) and BMI	87
Fig.(2)	Comparison between Cases and Controls regarding BMI categories	88
Fig.(3)	Comparison between Cases and Controls regarding BMI Z score	90
Fig.(4)	Comparison between Cases and Controls regarding ESR (mm/hr)	92
Fig.(5)	Comparison between Cases and Controls regarding hs-CRP (mg/L)	93
Fig.(6)	Comparison between Cases and Controls regarding S100A8/9 Protein (ng/ml)	94
Fig.(7)	Comparison between Cases and Controls regarding IGF-1 ng/ml	95
Fig.(8)	correlation between IGF-1 ng/ml and Weight (kg)	96
Fig.(9)	correlation between IGF-1 ng/ml and Height (cm)	97
Fig.(10)	correlation between IGF-1 ng/ml and BMII	97

Fig.(11)	correlation between IGF-1 ng/ml and S100 A8/9 Protein	98
Fig.(12)	correlation between S100 A8/9 Protein and Weight (kg)	99
Fig.(13)	correlation between S100 A8/9 Protein and Height (cm)	100
Fig.(14)	correlation between S100 A8/9 Protein and BMI	100
Fig.(15)	ROC curve for S100A8/9 Protein (ng/ml) in detection of Cases	101
Fig.(16)	ROC curve for IGF-1 (ng/ml) in detection of of cases	102