ROLE OF '14_3_3 ETA PROTEIN' IN PSORIATIC ARTHRITIS

Thesis

Submitted for partial fulfilment of master degree in Physical Medicine, Rheumatology and Rehabilitation

Introduced by

Sally Saber Abd Elaziz
M.B.B., B.Ch.
Faculty of Medicine, Ain shams University

Under Supervision of

Prof. Dr. Nahed Mouneir Sherif

Professor and head of Physical Medicine, Rheumatology and Rehabilitation department
Faculty of Medicine, Ain shams University

Prof. Dr. Henaz Farouk Khaled

Professor of Physical Medicine, Rheumatology and Rehabilitation
Faculty of Medicine, Ain shams University

Assist. Prof. Eman Ahmed Tawfik

Assistant professor of Physical Medicine, Rheumatology and Rehabilitation
Faculty of Medicine, Ain shams University

Faculty of Medicine
Ain Shams University
2016


بسم الله الرحمن الرحيم
﴿ وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا ﴾
صدق الله العظيم
سورة النساء آية (١١٣)

Acknouledgement

First and foremost, I thank **God** *for helping and guiding me in accomplishing this work.*

I would like to express my heartiest acknowledgement to ***Prof. Dr. Nahed Mouneir Sherif***, Professor of Physical Medicine, Rheumatology and Rehabilitation, Ain Shams University, for her constructive suggestions, valuable guidance, and for her continuous support. I'm indebted to her for always being there to help and solve difficulties. I deem myself fortunate to work under her supervision.

My deepest appreciation to ***Prof. Dr. Henaz Farouk Khaled***, Professor of Physical Medicine, Rheumatology and Rehabilitation, Ain Shams University, for her concrete support and suggestions. I appreciate all her contributionand her great interest in this work. Her constructive comments will always be remembered.

I wish to express my deepest thanks and gratitude to Ass. ***Prof. Dr. Eman Ahmed Tawfik***, Assistant Professor of Physical medicine, Rheumatology and Rehabilitation, Ain Shams University, for her continuous and enthusiastic stimulation throughout the whole work. Thank you for all your advice, ideas and support.

My biggest thanks of all go to ***my family (my dear father, my dear mother, my brother and all of my sisters especially my soul mate; Nancy), friends, and colleagues*** for their remarkable patience, help, and prayers. Thank you for being there for me.

Sally Saber

List of Contents

List of Abbreviations

AS	Ankylosing spondylitis
ASK1.....	Apoptosis signal-regulating kinase 1
AT.....	Adipose tissue
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMD	Bone mineral density
BMI	Body mass index
BSA	Body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis'
CLA	Cutaneous lymphocyte associated antigen
CRD	Cysteine-rich domain
DC	Dendritic cells
DC.....	Degenerative changes
DEAE-C	Diethylaminoethyl cellulose
DIP	Distal interphalangeal
DMARDs	Disease-ModifyingAnti-RheumaticDrugs
EF	Enthesis fibrocartilage
EGF	Epidermal growth factor
ET	Extensor tendon
FAB.....	Focal absence of subchondral bone
FACIT	Functional Assessment of Chronic Illness Therapy
FGF	Fibroblast growth factor
FHL	Flexor hallucis longus

List of Abbreviations (Cont...)

FKHRL1	Fork head transcription factor 1
G-CSF	Granulocyte-colony stimulating factor
GPP	Generalizedpustularpsoriasis
GUESS	Glasgow Ultrasound Enthesitis Scoring System
HAQ	Health Assessment Questionnaire
HSPs	Heat shock proteins
ICAM-1	Intercellular adhesion molecule-1
IFN-γ	Interferon γ
IL-1.....	Interleukin 1 (
IL-1β	Interleukin 1β
IP.....	Interphalangeal joint,
KD	Kilo Dalton
KIR	Killer immunoglobulin-like receptor
M-CSF	Macrophage-colony stimulating factor
MMP	Matrix metalloproteinases
MMP	Metalloproteinase
MRI	Magnetic resonance imaging
MSS	Modified Steinbrocker scoring
MSUS	Musculoskeletal ultrasound
MT	Middle tumor
MTPs	Metatarsophalangeal joints
NAPSI	Nail psoriasis severity index
NK	Natural killer
NOS2.....	Nitric oxide synthetase 2
OA	Osteoarthritis

List of Abbreviations (Cont...)

OD	Optical density
PASI	Psoriasis Area Severity Index
PBMCs	Peripheral blood mononuclear cells
PDGF	Platelet-derived growth factors
PF.....	Periosteal fibrocartilage
PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
PKC	Protein kinase C
PRRs	Pattern recognition receptors
PS	Phosphatidylserine
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RANKL	Receptor activator of NFκB ligand
RBD	Ras binding domain
RF	Rheumatoid factor
SB.....	Sesamoid bone,
SC	Synovial cavity
SEC.....	Synovio-entheseal complexe
SF.....	Sesamoid fibrocartilage
SM	Synovial membrane
SpA	spondyloarthritis
TNF- α	Tumor necrosis factor alpha
TNFAIP3.....	TNF-induced protein 3
VAS	Visual analog scale

List of Abbreviations (Cont...)

VCAM-1..... Vascular adhesion molecule- 1

VEGF ..... Vascular endothelial growth factor

VP ..... Volar plate,

List of Tables

List of Figures

ROLE OF 14-3-3 ETA PROTEIN IN PSORIATI ARTHRITIS

Abstract

Background/Purpose: 14-3-3 proteins are a conserved family of 7 isoforms with diverse cellular functions found predominantly intracellularly. The 14-3-3η isoform is expressed extracellularly in the joints of patients with rheumatoid arthritis (RA) and expression in both serum and joint fluid correlates strongly with expression of metalloproteinases. 14-3-3η activates proinflammatory signalling cascades and inflammatory mediators relevant to the pathogenesis of RA.Psoriatic arthritis one of the destructive arthropathy and no specific marker is available for diagnosis.We investigate the possible role of 14-3-3 eta as a diagnostic and severity marker in PsA.

Methods: Assays to measure the levels of 14-3-3 eta protein in serum of 20 PsA patients and 10 healthy adults matched to both age and sex and compare the 14-3-3 eta levels in the two groups and comparing the levels with clinical severity indices including PASI, NAPSI and BASDAI score and also with laboratory investigations including ESR, CBC, CRP, FBG, kidney function tests, liver function tests and serum uric acid.

Results: significantly higher serum levels of 14-3-3 eta protein in PsA patients compared to the controls. Statistically significant positive correlation between 14-3-3 eta level and disease duration ($P<0.001$) denoting its possible role as a marker for chronicity. Statistically significant positive correlation between 14-3-3 eta levels and severity indices ($p<0.001$) (r 0.946) denoting its role as severity marker. Statistically positive correlation with ESR ($p<0.001$) (r 0.838) and CRP ($p<0.05$) (r 0.595) denoting its role as an activity marker.

Conclusion: Extracellular 14-3-3 eta protein has been described as PsA diagnostic, severity and activity biomarker with prognostic and therapy monitoring applications.

Key words: 14-3-3 eta protein, psoriatic arthritis (PsA), destructive arthropathy

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that develops in at least 5% of patients with psoriasis, and it occursin up to 1% of the general population ***(Henes et al., 2014).***

The onset of arthritis in relation to the psoriasis differs. In 60-80 % of the patients, the arthritis follows the onset of psoriasis by 10-20 years. In 15-20% of patients, the arthritis precedes the psoriatic skin lesions. Occasionally, arthritis and psoriasis appear simultaneously ***(Al Hammadi, 2014).***

The patterns of psoriatic arthritis involvement are variable but there are 5 main patterns: asymmetrical oligoarticular arthritis symmetrical polyarthritis, distal interphalangeal arthritis, arthritis mutilans, and spondylitis with or without sacroiliitis ***(Dalbeth et al., 2010).***

The inflammed synovium in psoriatic arthritis (PsA) resembles that of rheumatoid arthritis (RA), but is associated with less hyperplasia and cellularity compared with RA, and greater vascularity and higher tendency to synovial fibrosis. Unlike RA, PsA shows prominent enthesitis, with histological changes quite similar to that of other spondyloarthritides ***(Reece et al., 1999)***.

to the inflammatory arthritis, enthesopathy or enthesitis may develop which reflects inflammation at tendon or ligament insertions into bone, and is frequently observed at the attachment of the Achilles tendon and the plantar fascia to the calcaneus with the development of insertional spurs ***(Al Hammadi, 2014).***

Dactylitis with sausage digits is also commonly encountered and may be seen in as many as 35% of patients. Other signs include Skin lesions in the form of scaly, erythematous plaques; guttate lesions; lakes of pus; and erythroderma. The psoriatic skin lesions may also occur in hidden sites, such as the scalp which can be mistaken for dandruff, perineum, intergluteal cleft, and umbilicus ***(Al Hammadi, 2014).***

The diagnosis of psoriatic arthritis can be missed because the patients commonly presented by symptoms other than frank arthritis. The most sensitive and specific criteria which is available is the 'Classification Criteria for Psoriatic Arthritis' (CASPAR). It is easy to use and allows the diagnosis of psoriatic arthritis even if the rheumatoid factor is positive ***(Taylor et al., 2006).***

However, no specific marker is available for the diagnosis. Thus there is a need to search for such marker ***(MeaseandReich, 2009).***

A newly discovered protein named '14_3_3 eta protein' may be promising in this aspect. The 14_3_3 family of conserved regulatory proteins consists of seven isoforms. Under normal circumstances, these proteins exist as intracellular adapters that can either homo- or hetero-dimerise to form a cuplike structure known as the *amphipathic groove*, which allows them to interact with more than 200 intracellular proteins to modulate their activities. Interactions include an array of biological processes, such as protein trafficking and cellular signaling***. (Kilani et al, 2007).***

One isoform of these 14_3_3 family of proteins is the 14_3_3 eta protein. This isoform has been detected extra-cellulary in arthritis, and found to act as an extracellular ligand which induces factors that contribute to joint damage. It has also been found highly expressed in patients with erosive RA. Additionally, it strongly correlated with MMP-1 and MMP3 in synovial fluid and serum which further characterizes its biological expression and association with rheumatologic disease processes ***(Maksymowych et al, 2011).***

Because 14_3_3 eta protein is not normally found in the blood, when it is present in patients with RA, it appears that the body tries to clear it by mounting an immune response creating auto-antibodies to 14_3_3 eta protein which can be measured in the serum. The combined use of 14_3_3 eta protein, rheumatoid