Secondary fibromyalgia syndrome (FMS) in different rheumatic diseases: relation to clinical manifestations, laboratory features, disease activity and quality of life

Thesis

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Sarah M Sabry

Contents

List of abbreviations

A	
ACL:	Anti cardiolipin antibodies
ACPA:	Anti-cyclic citrullinated protein antibody
ACR:	American College of Rheumatology
Ag:	Antigen
AI:	Activity index
ALT:	Alanine transaminase
AM:	Antimalarials
ANA:	Antinuclear antibody
ANS:	Autonomic nervous system
Anti-CCP:	Anti-cyclic citrullinated peptide
Anti-dsDNA:	Anti double-stranded deoxyribonucleic acid
Anti-MCV:	Anti-mutated citrullinated Vimentin
anti-RNP:	Anti ribonucleoprotein
Anti-Scl70:	Anti Scleroderma 70
Anti-Sm:	Anti Smith antibody
aPL:	Antiphospholipid
APS:	Antiphospholipid syndrome
AS:	Ankylosing spondylitis
AST:	Aspartate transaminase
AVN:	Avascular necrosis
AZA:	Azathioprine
B	
BD:	Behçets disease
BDCAF:	Behcet's disease Current Activity Form
BDI:	Beck Depression Inventory
BILAG:	British Isles Lupus Assessment Group
C	
C3:	Complement 3
C4:	Complement 4
CAP:	Cyclic alternating pattern
CBC:	Complete blood count
CBT:	Cognitive behavioral therapy
CDAI:	Clinical Disease Activity Index
CHF:	Congestive heart failure
CI:	Chronicity index
CMP:	Complete metabolic profile
CNS:	Central nervous system
COMT:	Catechol-O-methyltransferase
CK:	Creatine kinase
CREST:	C, calcinosis; R, Raynaud's phenomenon; E,esophageal dysmotility; S, sclerodactyly; T, telangiectasia
CRP:	C-reactive protein
CSA:	Cyclosporine
CSF:	Cerebrospinal fluid
CT:	Computed tomography

CTGF:	Connective tissue growth factor
CVA:	Cerebrovascular accident
CVD:	Cardiovascular disease
CWP:	Chronic widespread pain
CYC:	Cyclophosphamide
D	
DAS28:	Disease Activity Score 28
DLCO:	Diffusing capacity for carbon monoxide
DLE:	Discoid lupus erythematosus
DMARDs:	Disease modifying anti-rheumatic drugs
DNIC:	Diffuse noxious inhibitory control
DPGN:	Diffuse proliferative glomerulonephritis
DSM-IV:	Diagnostic and statistical manual of mental disorders
dSSc:	Diffuse systemic sclerosis
DVT:	Deep venous thrombosis
E	
EBV:	Epstein-Barr virus
ECG:	Electrocardiogram
ECM:	Extracellular matrix
EEG:	Electroencephalography
EMG:	Electromyography
EOD:	Every other day
ER:	Endothelin receptor
ERA:	Endothelin receptor antagonist
ESR:	Erythrocyte sedimentation rate
EULAR:	European League Against Rheumatism
F	
FGF:	Fibroblast growth factor
FIQ:	Fibromyalgia Impact Questionnaire
FIQR:	Revised Fibromyalgia Impact Questionnaire
FMF:	Familial Mediterranean fever
FMS:	Fibromyalgia syndrome
FPGN:	Focal proliferative glomerulonephritis
FTP:	Fingertip-to-palm distance in flexion
FVC:	Forced vital capacity
G	
GABA:	Gamma aminobutyric acid
GC:	Glucocorticoid
GERD:	Gastro-esophageal reflux disease
GFR:	Glomerular filtration rate
GGT:	Gamma glutamyl transferase
GIT:	Gastrointenstinal tract
gm/dl:	Gram/deciliter
GM-CSF:	Granulocyte-macrophage colony-stimulating factor
GN:	Glomerulonephritis

H	
HAQII:	Health Assessment Questionnaire II
Hb:	Hemoglobin
hCMV:	Human cytomegalovirus
HCQ:	Hydroxychloroquine
HCV:	Hepatitis C virus
HDGC:	High dose glucocorticoids
HLA:	Human leukocyte antigen
HRCT:	High-resolution computed tomography
HSP:	Heat Shock Protein
Hx:	History of
I	
IBS:	Irritable bowel syndrome
IC:	Immune complexes
ICBD:	International Criteria for Behçet's Disease
IFN-α:	Interferon alpha
Ig:	Immunoglobulin
IL:	Interleukin
ILD:	Interstitial lung disease
IM:	Intramuscular
IP:	Interphalangeal
IPL:	Inferior parietal lobule
ISG:	International Study Group
ISN/RPS:	International Society of Nephrology/Renal Pathology Society
IV:	Intravenous
L	
LAC:	Lupus anticoagulant
LBP:	Low back pain
LDGC:	Low dose glucocorticoids
LFN:	Leflunomide
lSSc:	Limited systemic sclerosis
LVEF:	Left ventricular ejection fraction
M	
mAb:	Monoclonal antibody
MAGIC:	Mouth and genital ulcers with inflamed cartilage
MAOIs:	Monoamine oxidase inhibitors
MBL:	Mannose-binding lectin
MCH:	Mean corpuscular hemoglobin
MCHC:	Mean corpuscular hemoglobin concentration
MCP:	Metacarpophalangeal
M-CSF:	Macrophage colony stimulating factor
MCV:	Mean corpuscular volume
MetS:	Metabolic syndrome
mg/dl:	Milligram/deciliter
MHC:	Major histocompatibility complex
MMF:	Mycophenolate mofetil
MNC:	Minocycline
MP:	Methylprednisolone
MRA:	Magnetic Resonance Angiography

MRI :	Magnetic Resonance Imaging
MRV:	Magnetic Resonance Venography
MRS:	Magnetic resonance spectroscopy
mRss:	Modified Rodnan skin score
MTP:	Metatarsophalangeal
MTX:	Methotrexate
N	
NAA:	N-acetylaspartate
NETs:	Neutrophil extracellular traps
NMDA:	N-methyl-d-aspartate
non-REM:	Non-rapid eye movement
NPSLE:	Neuropsychiatric systemic lupus erythematosus
NSAID:	Nonsteroidal anti-inflammatory drugs
O	
OA:	Osteoarthritis
P	
PA:	Postero-anterior
PAH:	Pulmonary arterial hypertension
PAS:	Patient Activity Scale
PCV:	Packed cell volume
PDE5-I:	Phosphodiesterase-5 inhibitor
PDGF:	Platelet-derived growth factor
PET:	Positron emission tomography
PFT:	Pulmonary function testing
PIP:	Proximal interphalangeal
PLT:	Platelet
PM	Polymyositis
PMR:	Polymyalgia rheumatica
PN:	Peripheral neuritis
PO:	Orally
PTSD:	Post-traumatic stress disorder
P value	Probability value
Q	
QoL	Quality of Life
R	
RA:	Rheumatoid arthritis
RAPID3:	Routine Assessment of Patient Index Data 3
RBC:	Red blood cell
RCTs:	Randomized controlled trials
RF:	Rheumatoid factor
RNA:	Ribonucleic acid
ROM:	Range of motion
RP:	Raynaud's phenomenon
RPGN:	Rapidly progressive glomerulonephritis
RV:	Rheumatoid vasculitis

S	
S:	Serum
SAS:	Sulfasalazine
SC:	Subcutaneous
SCLE:	Subacute cutaneous lupus erythematosus
SD:	Standard deviation
SDAI:	Simplified Disease Activity Index
SF-36	Medical outcomes study Short Form-36
SI:	Symptom Intensity scale
SIJ:	Sacroiliac joint
SJC:	Swollen joint count
SLAM:	Systemic Lupus Activity Measure
SLE:	Systemic lupus erythematosus
SLEDAI:	Systemic Lupus Erythematosus Disease Activity Index
SLICC:	Systemic Lupus International Collaborating Clinics
SNEC:	Secondary necrotic cells
SNRIs:	Serotonin and noradrenaline reuptake inhibitors
SpA:	Spondyloarthritis
sPAP:	Estimated pulmonary artery systolic pressure by Doppler echo
SRC:	Scleroderma renal crisis
SS:	Symptoms Severity
SSc:	Systemic sclerosis
SSRIs:	Selective serotonin reuptake inhibitors
STAI:	State-Trait Anxiety Inventory
STG:	Superior temporal gyrus
STP:	Superficial thrombophlebitis
T	
T2T:	Treat-to-target
T3:	Tri-iodothyronine
T4:	Thyroxine
TCAs:	Tricyclic antidepressants
TGF:	Transforming growth factor
Th:	T helper cells
TJC:	Tender joint count
TLR:	Toll-like receptor
TMA:	Thrombotic microangiopathy
TNF:	Tumor necrosis factor
TPs:	Tender points
TSH:	Thyroid Stimulating Hormone
TSS:	Total skin thickness score
TTP:	Thrombotic thrombocytopenic purpura
U	
ULN:	Upper limit of normal
W	
WBC:	White blood cells
WHO:	World health organization
WPI:	Widespread pain Index
Wt:	Weight

List of tables

List of figures

Abstract

Objective: To detect and compare the frequency of secondary fibromyalgia syndrome (FMS) in different rheumatic diseases; rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Behçets disease (BD) and to study the relation of FMS to the clinical manifestations, laboratory features, disease activity and/or damage as well as the quality of life (QoL).

Patients and methods: The study group included 160 patients (50 RA, 50 SLE, 30 SSc and 30 BD) and 141 age and sex matched controls for each corresponding disease. All patients were subjected to full history taking, physical examination, relevant investigations, assessment of disease activity using Disease Activity Score in 28 joints (DAS28) for RA, SLE Disease Activity index (SLEDAI), modified Rodnan skin score (mRss) for SSc and BD Current Activity Form (BDCAF), functional status assessment using Health Assessment Questionnaire II (HAQII) in RA, Systemic Lupus International Collaborating Clinics/ Damage Index (SLICC/DI) in SLE and severity scale in SSc. Quality of Life (QoL) scale was also recorded. The frequency of FMS was determined using 2010 ACR criteria. Severity in FMS cases was performed using the revised Fibromyalgia Impact Questionnaire (FIQR) score.

Results: In the RA, SLE, SSc and BD patients, FMS was found in 14%, 18%, 6.67% and 3.33% respectively compared to their corresponding controls (2.1%, 3%, 3.3% and 0% respectively). In RA patients, DAS28 was significantly higher in the RA patients with FMS ($p= 0.009$) and significantly correlated with both Widespread Pain Index (WPI) ($p = 0.011$) and Symptom Severity (SS) scale ($p = 0.012$). In SLE patients, both SLEDAI and SLICC/DI were not significantly different between SLE patients with and without FMS ($p = 0.6$ and $p = 0.32$ respectively). However, SLEDAI and SS scale were correlated ($p = 0.05$). In SSc patients, WPI and SS scale were not correlated with mRss or with severity scale. In BD patients, BDCAF score and WPI significantly correlated ($p = 0.03$).

Conclusion: Fibromyalgia syndrome (FMS) is present in different rheumatological diseases in higher percent than the normal individuals and could be related to the disease activity in RA, SLE and BD patients.

Key words: Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Systemic sclerosis (SSc), Behçets disease (BD), fibromyalgia syndrome (FMS), Disease Activity, Damage.

Introduction

Fibromyalgia syndrome (FMS) is a clinical syndrome that is defined by the presence of generalized pain, fatigue, unrefreshed sleep, multiple somatic symptoms and cognitive problems **(Cazzola et al, 2008).** The 1990 American College of Rheumatology (ACR) criteria for FMS require that an individual has both a history of chronic widespread pain (CWP) and the presence of 11 or more of 18 possible tender points on examination **(Wolfe et al, 1990).** In 2010 and 2011, alternative criteria for FMS were established that did not require performing a tender point count. These new criteria are aligned with a more contemporary view of the "pain centralization phenotype" which acknowledges that the most discriminating features of FMS are combined with other comorbid symptoms such as fatigue, memory difficulties as well as sleep and mood disturbances **(Wolfe et al, 2010 and Wolfe et al, 2011a).**

Rheumatological diseases are generally chronic and this is often reflected in the onset and persistence of symptoms such as pain, whose physiopathological characteristics may change over time. It has been known for some time that as many as 15-30% of patients with classic autoimmune or rheumatic disorders also have a co-morbid FMS, known as "secondary FMS" **(Atzeni et al., 2011).** As these rates are much higher than the prevalence of FMS in the general population (2%), it seems that the pain and/or stress accompanying chronic rheumatic diseases is also capable of triggering conditions such as FMS **(Sarzi-Puttini et al., 2011).**

Concomitant FMS is a common clinical problem in rheumatologic diseases, and its recognition is important for the optimal management of these diseases. Increased pain, physical limitations, and fatigue may be interpreted as increased activity of these diseases, and a common treatment option is the prescription of higher doses of corticosteroids or biologic agents **(Haliloglu et al., 2014).**

Aim of the work

The aim of the present work is to detect and compare the frequency of secondary fibromyalgia syndrome (FMS) in different rheumatic diseases; Rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE), Systemic sclerosis (SSc) and Behçet's disease (BD). The work also studied the relation of FMS to the clinical manifestations, laboratory features, disease activity and quality of life (QoL) and the relation of FMS to disease damage in SLE and SSc.