FIBROMYALGIA; UPDATED CONCEPTS

Review Article

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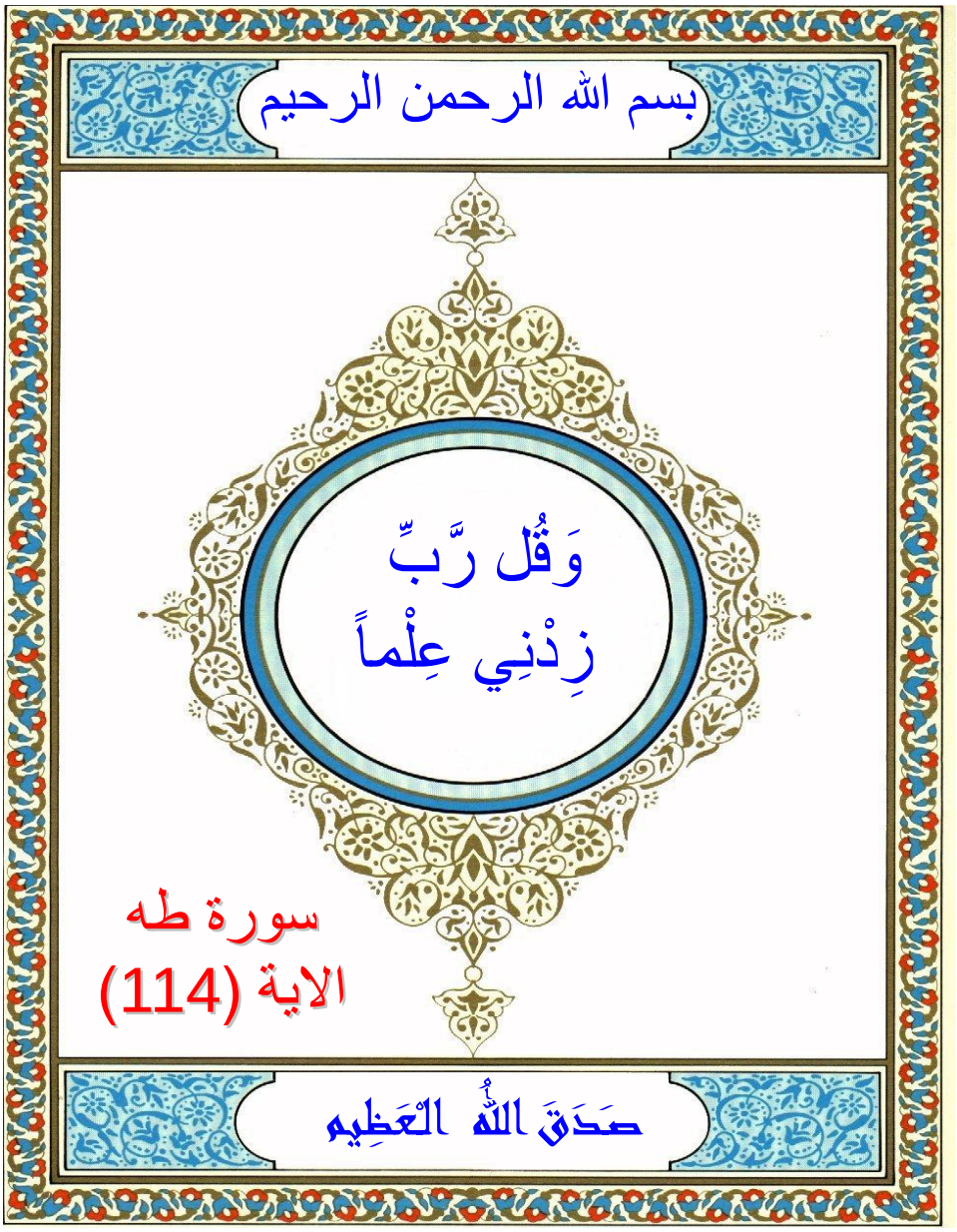
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List of Abbreviations

5-HT3	*5-hydroxytryptamine*
ACR	*American College of Rheumatology*
ACTH	*Adrenocorticotropic hormone*
AE	*Aerobic exercise*
ANS	*Autonomic nervous system*
APF	*American Pain Foundation*
CBT	*Cognitive behavioral therapy*
CFS	*Chronic fatigue syndrome*
CNS	*Central nervous system*
CWP	*Chronic widespread pain*
DLF	*Dorsolateral funiculus*
DLP	*Dorsolateral pontine cell groups*
DSM-IV	*Diagnostic and Statistical Manual-IV*
EMG	*Electromyogram*
FDA	*Food and Drug Administration*
FIQ	*Fibromyalgia Impact Questionnaire*
fMRI	*Functional magnetic resonance imaging*
FMS	*Fibromyalgia syndrome*
FSS	*Functional somatic syndrome*
GABA	*γ-aminobutyric acid*
GH	*Growth hormone*
HPA	*Hypothalamic–pituitary–adrenal*
HPG	*Hypothalamic–pituitary–gonadal*
HRV	*Heart rate variability*
IGF-1	*Insulin-like growth factor-1*
IL	*Interleukin*

MORs	*Mu-opioid receptors*
NG/NC	*Nuclei gracilis and cuneiformis*
NK-1	*Neurokinin 1*
NMDA	*N-Methyl-D-aspartate*
NSAIDs	*Nonsteroidal Antiinflammatory Drugs*
PAF	*Peripheral afferent fibers*
PAG	*Periaqueductal gray*
PTSD	*Posttraumatic stress disorder*
QOL	*Quality of life*
rCBF	*Regional cerebral blood flow*
RCT	*Randomized controlled trial*
RVM	*Rostral ventromedial medulla*
SCID	*Structured Clinical Interview for DSM-IV*
SF-36	*Short Form 36*
SNRIs	*Norepinephrine reuptake inhibitors*
SPECT	*Single photon emission computed tomography*
SSRIs	*Selective serotonin reuptake inhibitors*
STT	*Spinothalamic tract*
TLR4	*Toll-like receptors 4*
TrP	*Trigger points*
VAS	*Visual analog scale*

INTRODUCTION

Fibromyalgia Syndrome is a chronic disorder characterized by abnormal pain, fatigue, and sleep disturbance. The body's immune, hormonal, and nervous systems are involved ***(Frenger, 2009)***. It is a common functional somatic syndrome having prevalence of 2% to 7% of the population and affecting predominantly middle-aged women ***(Sumpton and Moulin, 2008)*.**

Fibromyalgia is considered a multifactorial disorder. Central nervous system sensitization is a major patho-physiological aspect of fibromyalgia ***(Ablin et al., 2008)***. Environmental and genetic factors play a role in the pathogenesis of FMS. Various triggers including trauma and stress as well as infections, may precipitate the development of FMS. Certain infections including hepatitis C virus, HIV and Lyme disease have been temporally associated with the development of FMS ***(Buskila et al., 2008)***.

Neurotransmitter studies show that fibromyalgia patients have abnormalities in dopaminergic, opioidergic, and serotoninergic systems which involved in modulating pain perception and central analgesia in patients with fibromyalgia. In other neuronal pathways in the brain, the same neurotransmitters are involved in mood control, sleep

regulation and cognitive function providing a neuro-chemical substrate for the wide range of symptoms seen in fibromyalgia ***(Stahl, 2009)*.**

The key feature of fibromyalgia is a chronic pain picture located in different structures of the musculoskeletal system, but without any evidence of disease in them and is thus fundamentally different from rheumatic disorders and many other pain conditions. Besides pain, patients with fibromyalgia often describe tiredness, sleep disorders, chronic headache, and emotional problems, as well as many other psychosomatic complaints ***(Arias, 2008).***

Many patients experience cognitive dysfunction (known as "brain fog" or "fibrofog"), which may be characterized by impaired concentration, problems with short and long-term memory, diminished attention span, anxiety, and depressive symptoms ***(Buskila and Cohen, 2007).***

Other symptoms often attributed to fibromyalgia that may possibly be due to a co-morbid disorder include myofacial pain syndrome, irritable bowel syndrome, restless leg syndrome, irritable bladder syndrome, dermatological disorders, numbness and tingling sensations. Muscle twitching and eye problems can also be a symptom of the condition ***(Russell and Raphael, 2008).***

Diagnosis of fibromyalgia requires presence of history of widespread pain lasting more than three months—affecting all four quadrants of the body, i.e., both sides, and above and below the waist, and tender points — there are 18 designated possible tender or trigger points (around the neck, shoulder, chest, hip, knee, and elbow regions), the patient must feel pain at 11 or more of these points for fibromyalgia to be considered ***(Clauw, 2008).***

Differential diagnosis of FMS includes polymyalgia rheumatica, myofascial pain, connective tissue disease, endocrine myopathies, psychoneuroses, and other chronic fatigue syndromes ***(Hwang and Barkhuizen, 2006)***.

As in other chronic pain syndromes, a multidimensional approach optimizes treatment response. Empirical data and consensus support the use of none pharmacological modalities, such as education, aerobic exercise, and cognitive behavioral therapy in the management of fibromyalgia. Evidence-supported pharmacological interventions include; tricyclic antidepressants, selective serotonin reuptake inhibitors, and other serotonergic-noradrenergic, analgesic agents, such as tramadol, nonsteroidal anti-inflammatory drugs, and anxiolytics and sleep aids. Serotonin-norepinephrine reuptake inhibitors such as Duloxetin and anti-seizure medication such as Pregabalin were recently approved in the United States for treatment of fibromyalgia ***(Huynh et al., 2008).***

AIM OF THE WORK

To discuss pathogenesis, characteristic clinical presentation and management of fibromyalgia and emphasis the idea that fibromyalgia is a neurological disorder.

EPIDEMIOLOGY & ETIOPATHOLOGY OF FIBROMYALGIA

History

Clinical description of fibromyalgia has been reported since mid-1800s. In 1904, Sir William Gowers created the term "fibrositis" when he was actually referring to regional pain syndrome ***(Gowers, 1904).*** The term "fibrositis" hence was a misnomer and no longer used as studies have shown that there were no inflammation within the connective tissues. "Fibromyalgia" was first introduced in 1976 in an editorial to the section on non-articular rheumatism in the 22nd "Rheumatism Review" of the American Rheumatism Association (currently known as ACR). Derived from both Latin (fibra – fiber) and Greek words (myo-muscle and algos–pain), it literally means "pain in the muscle and fibrous tissues" ***(Yunus and Kalyan-Raman, 1989).***

Epidemiology

FMS is a very common condition, estimated to affect 2% to 4% of the population ***(Lawrence et al., 2008)*** although local epidemiologic study is lacking. It has a prevalence of 3.4% in women versus only 0.5% in men with a female-to-male ratio of approximately 9:1. Usually diagnosed between 20 to 50 years of age, it increased with

age until aged 70 after which it decreased slightly. FMS can also occur in children at prevalence rate of 1.2% and 1.4% ***(Buskila et al., 1995).***

The prevalence of FMS is considerably higher in rheumatology clinic at 12% to 20% of new patients seen whereas it occurs in 5% to 6% of adult patients presenting at general medical and family practice clinics ***(Hughes et al., 2006).***

In a recent European survey in France, Germany, Italy, Portugal, and Spain, The estimated overall prevalence of FM was 4.7% ***(Branco et al., 2010).***

Etiology and Pathogenesis

The etiology of FM remains unknown, and the findings of studies of its potential pathophysiological mechanisms are conflicting. FM patients lack consistent tissue abnormalities and show features of hyperalgesia (increased sensitivity to painful stimuli) and allodynia (a lowered pain threshold). Emerging evidence points toward augmented pain processing within the central nervous system (CNS) as having a primary role in the pathophysiology of this disorder ***(Staud and Spaeth, 2008).***

The primary pathophysiology in FM engages interactions between genetic and environmental factors. A surge of physiological, psychological, behavioral, and

cognitive factors in FM interact to manifest in various symptoms and comorbidities ***(Williams and Clauw, 2009).***

- ***Genetics***

Recent evidence suggests that genetic factors may play a role in the pathogenesis of FM ***(Buskila, 2007).*** Certain environmental factors (stressors) may trigger the development of FM in genetically predisposed individuals ***(Clauw and Crofford, 2003).***

A number of studies published over recent years have documented increased prevalence of FM among family members of patients suffering from this syndrome. ***Buskila and colleagues (1996)*** found that 28% of offspring of FM patients fulfilled the 1990 ACR classification criteria for the diagnosis of FM. The authors have further reported that the prevalence of FM among blood relatives of patients with FM was 26%, and that the FM prevalence in male and female relatives was 14% and 41%, respectively ***(Buskila and Neumann, 1997).***

Arnold and colleagues (2004) reported that FM aggregates strongly in families: the odds ratio measuring the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with rheumatoid arthritis was 8.5. Research performed in recent years has demonstrated a role for polymorphisms of genes in the