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GENETICS AND PATHOPHYSIOLOGIC QUANDARY OF FIBROMYALGIA: NATURE VERSUS NURTURE.

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ABSTRACT

Background: Fibromyalgia (FM) is a multifactorial neurological disorder associated with chronic extensive pain that belongs to an extended family known as Affective Spectrum Disorders (ASDs). Pathophysiology of fibromyalgia includes abnormalities in the neuroendocrine, autonomic nervous systems, genetic factors, psychosocial variables, and environmental stressors. These abnormalities are involved in other disorders, such as irritable bowel syndrome and temporomandibular disorder. In fact, fibromyalgia refer to central augmentation of sensory input rather than central sensitization of pain. Genetic researches explain the variability in the perception of pain. Recent evidence suggests a role for the genetic polymorphisms in the serotoninergic, dopaminergic and catecholaminergic systems in the pathogenesis of FM pain. The interplay between genetic and environmental risk factors may strengthen the breakthrough mechanism in understanding the pathogenesis of FM. Francis Galton on 1875 invented the term "nature (genes) versus nurture (environment)" to explain the interindividuals variability of pain using twin studies. **Conclusion:** Investigations indicate that the most likely way of inheritance of FM is polygenic; it's not means minimizing the role of monogenic mendelian mode of inheritance of pain. Sophisticated genetics technology is warranted to get on shared biological mechanism of the pathways of nociception and to

enlighten the heritability in pain differences and the susceptibility to pain and its related components such as the pathophysiology and behavioral disturbances. Indeed, well-made genetic and epigenetic investigations in the field of human pain will help to estimate risk factors manipulating pain perception and how they can be influenced via epigenetic processes. The novel technologies using genome-wide association study can reveal gene loci and signaling pathways and the Micro RNAs are progressively more harnessed for the study of the chronic pain and the pathogenesis of FM. When we completely elucidate the nature and nurture of human pain, we will be able to control it. This manuscript comes to shed light on the pathogenesis of a discreet complex condition, difficult to diagnose, characterized by pain centralization and chronification.

KEYWORDS: Fibromyalgia; Affective Spectrum Disorders; polygenic disorder; neurotransmitters and hormones.

INTRODUCTION

Fibromyalgia (FM) called formerly fibrositis is a multifactorial neurological disorder produces chronic extensive widespread musculoskeletal aching pain, general fatigue, poor sleep, and exhaustion from head to toe, which continues throughout an individual's lifetime and it, is non-life threatening disorder. FM belongs to an extended family known as Affective Spectrum Disorders (ASDs) that frequently co-appear in individuals and co-aggregate among families, means congregating or clustering of pairs of disorders, where one of the two pairs is almost always major depressive disorder (MDD). Communally, a considerable co-aggregation of MDD with other ASDs was confirmed in different studies and in twin studies.[1-7]

ASDs share physiologic abnormalities, genetic risk factors, in addition to environmental factors that may be central to their etiology. The English scientist Francis Galton on 1875 invented the term "nature (genes) versus nurture (environment)" to explain the interindividuals variability of pain using twin studies and since that time the term is used to describe the interaction between environmental and genetics risk factors to study complex diseases.[8]

ASDs by lumping together plethora of neuropsychiatric disorders and a few physical disorders of unknown etiology, sharing a multiple overlapping and intertwined common clinical background symptoms and by responding to the same type of therapeutic regime

make them unique disorders. This harmony between these disorders increases the prediction and the assumption that these spectrum disorders sharing also common pathogenesis or heritable pathophysiological features.

ASDs cover more than 10 neuropsychiatric disorders and 4 medical conditions and beneath the umbrella of ASDs, arrays of neuropsychiatric disorders and medical conditions are mounted up; especially major depression, posttraumatic stress disorder, Burnout syndromes, attention- deficit/hyperactivity disorder, obsessive-compulsive disorder, anancastic & borderline personality disorder, social phobia, bulimia, anxiety disorder, panic disorder, premenstrual dysphoric disorder and medical co-morbidities such as migraines, cataplexy-narcolepsy and irritable bowel syndrome in addition to our vanguard one; the fibromyalgia respectively.[9,10]

The term *Fibromyalgia* encompasses three components: the first comes from the Latin [(fibrous tissue (*fibro*)]; the second comes from Greek [(for muscle (*myo*)] and the third refers to pain (*algia*). Historically, this complex medical condition was described since 1800s as "muscle pain rheumatism" and on 1981 the American rheumatologist used the term "muscle and connective tissue pain" to define this complex condition.[11]

Indeed, the precise underpinning etiology of fibromyalgia still ambiguous, but overabundance of theories was proposed, indicating that both physically and emotionally factors play a cardinal rule in its causation. The nature of the widespread fibromyalgia pain also remains in the border of speculations. This multifaceted disorder is a chronic phenomenon considered to epitomize a paradigm of centralized pain that decreases the quality of life and affects sufferers physically, psychologically, and socially.

FM comprises of a set of symptoms and occurs worldwide, without ethnic tendency. It affects approximately over 6 million individuals in the United States, 90% of them is females (females/males approximate ratio of 9:1). Symptoms generally encountered between 20-55 years of age. In Europe, researchers estimate 14% prevalence mainly in females, which means that FM runs in females more often than males. A notable high prevalence of FM was encountered among offspring of FM mothers; this fact may be credited to genetic factors.[12]

The fibromyalgia pain may migrate over the body causing tenderness of muscles, joints, and tendons which tend to have remitting and relapsing pain course over time. Patients with

fibromyalgia have been suffered from numerous concomitant medical and psychiatric illnesses, that have negative impact on other body systems (tender points) by causing restless sleep, intense fatigue, tiredness, depression, gastrointestinal disturbances, flu like symptoms and mimic other diseases such as hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, polymyalgia rheumatic, and neuropathies.[7]

It was thought that it may be due to abnormalities in the distributions and dysfunctional pain processing of the central sensory input accompanied by alterations in internal cerebral pathways responsible for inhibition of pain.

In fact, the hypersensitivity to pain or the lower threshold for pain, the Hyperalgesia and the Allodynia observed in the sufferers of fibromyalgia may be related to the fact that these individuals may have the inability to cope with embarrassing situations such as facing unpredictable physical, social, emotional, or psychological pressures.[13]

Biologic abnormalities related to neuroendocrine system disturbances such as inadequate function of the hypothalamic-pituitary-adrenal (HPA) axis which is involved in acute and chronic pain and increase levels of cortisol, which are thought to be rebound negatively on stress-related disorders such as fibromyalgia is a worthy example.[14]

In addition, the ineffective endogenous biological feedback responses in the autonomic nervous system and the low levels of neurotransmitters serotonin and norepinephrine and increase levels of neuropeptide (substance P) that are implicated in the transmission of pain signals to the CNS, conceivably are also involved in pain mechanism and they may explain partially the underlying causes of fibromyalgia pain; taking into account the decreased correlation between cerebral pain centers and sensory-motor cerebral brain network regions that finally lead to inadequate neural activity, lack of pain inhibition and alteration in pain perception, are also playing critical role in the mechanism of pain. This disconnection and negative interactive between the two centers; the central sensory input and the internal cerebral pathways responsible for inhibition of pain, could be considered as a faulty mechanism responsible for pain irregularity encountered in fibromyalgia.[15,16]

Relationship between Genetic and Fibromyalgia

Although the way of inheritance of FM is mysterious and multifactorial, the role of the epigenetic is to serve as viaduct between nature and nurture by conducting a mechanism not intrinsic to the genetic code by which the nurture (environment) can in a straight line regulate the translation of the DNA information into proteins via heritable changes in gene function, but affect gene expression in a tissue-specific manner, resulting in a specific phenotype.[17]

This role is becoming progressively central in regards to fibromyalgia pain development. In fact, beside the assumption that polygenic inheritance underlies this multifaceted disorder, genetic susceptibility of individuals to develop FM generally request undetermined environmental trigger factors, which may be emotional and mechanical trauma. Further factors that could trigger the disorder include autoimmune diseases, stressful life, various histories of infectious illnesses, or even allergies to particular food and intoxication from different materials.[18,19]

Recent researches, suggested a role of the genetic polymorphisms and abnormalities in genes that are related to the neurotransmitters and hormones that have been verified to be connected to the pathogenesis of FM pain and other related conditions. These genes include the serotoninergic, glutamatergic, dopaminergic and catecholaminergic systems. Serotonin has a vital function in the CNS; abnormalities of this crucial neurotransmitter based on its probable involvement in the pathophysiology of FM may create ominous problems especially psychiatric problems.[20,21]

In fact, owing to potential genetically driven susceptibility of serotonergic dysfunction in FM such as serotonin transporter (5-HTT) and serotonin 2A (5-HT2A), a single nucleotide polymorphism (T102 allele of the 5-HT2A-receptor) in the serotonin transporter (*5-HTT*) gene was examined and the results illustrates that this polymorphism may provoke increase pain sensitivity and may be implicated in the complex path of nociception among individuals with fibromyalgia and other ASDs. In fact, studies showed frequent association between FM and the regular polymorphisms in the promoter area of the serotonin transporter gene (SLC6A4) as well as other disorders.[22-24]

Indeed, Offenbaecher and colleagues (Offenbaecher et al., 1999) and (Lee et al., 2010) investigated the genotypes of the serotonin transporter promoter locus (5HTTLPR) in fibromyalgia patients, and they also observed that (S/S genotype) in the regulatory region of the 5-HTT occurred more frequently in FM patients (31%) than healthy individuals (16%).

The association between fibromyalgia and 5-HTTLPR polymorphism was also replicated by cohen et al, 2002. However, other studies were inconsistent with this findings.[20, 25-30]

As a result of the 5HTTLPR genetic association in some personality mood and in various human disorders in addition to its role in the regulation of the serotoninergic neurotransmission, raise its scores as a promising candidate gene in fibromyalgia, by its polymorphism or by its indirectly involvement in FM.[31,32]

Furthermore, well-advanced studies in the idiopathic pain gene (COMT gene), which occupied great responsibility in the pathogenesis of neuropsychiatric disorders, are underway to investigate the genetic polymorphism of [(Catechol-O-methyltransferase (*COMT*)], its role in the process of inactivation of catecholamines (dopamine, epinephrine, and norepinephrine) neurotransmission, and its task in causing a variations in experimental and clinical pain behavior.[33]

Moreover, FM is associated with a neuroendocrine dysfunction due to irregular activity of the hypothalamic-pituitary-adrenal (HPA) axis, comprising overproduction of adrenocorticotropic hormone (ACTH) leading to increase its concentration in blood stream and causing adrenal malfunction. Beside the activity of COMT enzyme to terminate the production of catecholamines, it is also involved in abolishing the drugs containing catecholamines. Gursoy et al, reported a study comparing the three polymorphisms of the COMT gene (LL, LH, and HH) among 61 cases versus 61 healthy. The authors reported no significant difference was found between LL and LH polymorphism separately and when they genotypes LL and LH together they were significantly represented in patients than controls. Consequently when HH were genotypes in patients they were significantly lower than in the control groups. These results stress the importance of COMT polymorphism in the pathogenesis and pharmacological treatment of FM.[34-37]

Reviewing the literature, studies reported that decrease COMT activity is associated with exacerbate the hypersensitivity to acute pre-surgical and postsurgical pain. Tammimäki and Männistö 2012 reported a meta-analyses study, discussing the relationship between COMT polymorphism and various chronic pains. The results of the reported meta-analyses illustrate that FM or chronic widespread pain is the only sort of pain that could be linked with the COMT single nucleotide polymorphism – SNP: rs4680 (Val158Met, SNP in codon 158 of COMT gene, substitution of Valine for Methionine) and Met158, causing a decrease activity

of COMT enzyme to a 3-4 fold, and homozygousity observed in individuals with Met158 allele showed a deceased activity of mu-opioid system to pain. Indeed, polymorphism of COMT, Val158Met affects the individuals experience to pain and may perhaps underneath the differences in the variation in pain responses between individuals.[38]

These results were in concurrence with the study conducted by Martínez-Jauand et al, 2013. It has been shown that inadequate function of COMT may increases the risk for the appearance of FM. Indeed, the complicated relationship between catecholamines (adrenergic and dopaminergic) hyperactivity and their increase levels in various parts of the nociceptive system may elucidates the fact that complex actions of low activity of COMT is the underpinning cause of FM.[33, 39-42]

Further candidate genes such as DRD4 exon III 7 repeat genotype was studied by Buskila et al, using the same sample size used by Cohen et al. these researchers revealed a connection between FM and DRD4 exon III 7 gene.

The gene variant, DRD1, was 33% more common in the low pain group; COMT and OPRK were common among moderate pain group, their presence was 25% and 19% higher than the severe pain group respectively. The severe pain group, were 25% more likely to have the variant DRD2 than moderate group.

Malt et al, 2003 demonstrate the involvement of D2 receptor in FM, via increasing its sensibility and density, and Treister et al. 2009, found significant association between DAT1 polymorphism and the quantitative measure of cold tolerance.[20, 43-45]

However, previous studies demonstrate the efficacy of adequate activity of the dopaminerdic neurotransmission in the brain, and showed the consequences of its deficiency such as reward deficiency syndrome. Reward system is a collection of brain structures which attempts to regulate and control behavior by inducing pleasurable effects. The major neurochemical pathway of the reward system involves the mesocorticolimbic pathway (MCLP). The major chemical in the reward system is dopamine, and when we have a deficit or low dopaminergic activity of dopamine D2 (DRD2) Gene, and especially its allele Taq1 A1 and its receptor we encountered behavioral disturbances and high pain sensitivity.[20, 46-49]

Additionally, monogenic pain disorders or mendelian heritable pain disorders are involved in the pathogenesis of pain and may have breakthrough by providing broadly insights into pain

mechanisms. The first category is the gene SCN9A, which is responsible for three pain disorders in human: the primary erythermalgia, episodic paroxysmal pain disorder and complete pain absence disorder caused by nonsense mutations.[50-52]

Other autosomal recessive congenital disorder with insensitivity to pain was discovered, and 13 new SCN9A alleles have been reported yet. These finding may explain the variation for human pain and may underpin the different pain perception among general population.[53-54]

Another category including five types of hereditary sensory neuropathies (HSN: 1-5) located in different chromosomes was reported: HSN I (9q22.1–22.3); HSN II (12p13.33); HSN III (9q31); HSN IV (1q21-q22) and HSN V (1p13.1) respectively. These HSN genes may be involved in various pathological pain types.[55-61]

Familial hemiplegic migraine (FHN), with its three classes of a uncommon monogenic dominant autosomal disorder represent a special clinical spectrum caused by [(Mutations on CACNA1A gene at chromosome (19p13); (ATP1A2 gene at chromosome (1q23), and SCN1A gene at chromosome (2q24)] respectively, were also recognized as a pain disorders, and they represent a special entity of multifaceted channelopathy, with deficit on sodium and calcium channels.[62-64]

DISCUSSION

The interplay between genetic and environmental risk factors may strengthen the breakthrough mechanism in understanding the pathogenesis of FM inevitable pain and complex traits which still not wholeheartedly understood. The English scientist Francis Galton on 1875 invented the term “nature (genes) versus nurture (environment)” to explain the interindividuals variability of pain using twin studies. Since that time the term is still in used to describe the interaction between environmental and genetics risk factors related to complex diseases. Indeed, well-made genetic and epigenetic investigations in the field of human pain will help to estimate multifactorial risk factors manipulating pain perception and how they can be influenced via epigenetic processes.[65]

Speculation that the most likely way of inheritance of FM is polygenic, it’s not means minimizing the role of monogenic mendelian mode of inheritance of pain, recent family researches, suggested a role of the genetic polymorphisms and abnormalities in genes that are related to the neurotransmitters and hormones that have been verified to be connected to the

pathogenesis of FM pain and other psychiatric co-morbidities. These genes include the serotoninergic, glutamatergic, dopaminergic and catecholaminergic systems.

Certain polymorphisms act to increase pain; the most recent genes of interest include *KCNS1*, *SCN9A*, *ADRB2*, *H2TRA*, *CACNG2*, and *IL16*. Another family of alleles has been identified as conferring pain protection; such as COMT, *OPRM1*, *TRPV1*, *MC1R*, *GCH1*, and *CACNA2D3*.

However, affective spectrum disorders by sharing a multiple overlapping and intertwined common clinical background symptoms and by responding to the same type of therapeutic regime make them unique disorders. This harmony between these disorders increases the prediction and the assumption that these spectrum disorders sharing also common pathogenesis or heritable pathophysiological features.

Sophisticated genetics technology will help investigators to get on underlying shared biological mechanism of the pathways of nociception underneath pain and to enlighten the heritability in pain differences and the susceptibility to pain and its related components such as the pathophysiology and behavioral disturbances. The novel technologies using genome-wide association study (GWAS) can reveal gene loci and signaling pathways connected with a known pain phenotype and Micro RNAs which a posttranscriptional inhibition of gene expression, are progressively more harnessed for the study of the chronic pain and the pathogenesis of FM. When we completely elucidate the nature and nurture of human pain, we will be able to control it.

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