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Review

Pathogenesis of fibromyalgia – A review

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Abstract

Fibromyalgia, a syndrome characterized by widespread pain and diffuse tenderness, is considered a multifactorial disorder. Central nervous system sensitization is a major pathophysiological aspect of fibromyalgia, while various external stimuli such as infection, trauma and stress may contribute to development of the syndrome. In addition, current evidence points towards the existence of a genetic basis for fibromyalgia and information has been accumulated regarding the role of a number of candidate genes in fibromyalgia pathogenesis. In the present review, we have summarized the clinical manifestations of fibromyalgia, as well as the necessary laboratory workup; subsequently we have attempted to cover various aspects of pathogenesis with special emphasis on the genetic aspects currently uncovered.

Keywords: Fibromyalgia; Pathogenesis; Central sensitization; Genetics

1. Introduction

Fibromyalgia seems to be here to stay. Although coined as a nosological entity only some two and a half decades ago, and adorned official American College of Rheumatology (ACR) criteria only in 1990 [1], patients suffering from syndromes such as ''fibrositis'' and ''soft tissue rheumatism'' have been described in medical literature for over a century [2]. In the past, we have witnessed spirited debates regarding the classification, pathogenesis and mere validity of the concept of fibromyalgia [3,4]. Thousands of research articles published on the topic attest to the great interest drawn to the syndrome, which is estimated to affect a staggering 2% of the population. Significant progress has occurred over recent years regarding our understanding of the mechanisms underlying altered pain processing characteristic of fibromyalgia; this evolution of knowledge is leading towards novel strategies for management of fibromyalgia pain. As our knowledge regarding the pathogenesis and etiology of fibromyalgia increases, the historical debate regarding validity is likely to be replaced by an effort to better classify patients, to identify subgroups with unique clinical characteristics and to pinpoint therapeutic interventions, while decreasing the daunting side effects of current empirical treatment. In the following review, we shall attempt to describe what is currently known about the pathogenesis of fibromyalgia and special attention will be directed towards the genetic basis of this evidently multifactorial, intriguing syndrome.

2. Clinical presentation

ACR criteria define fibromyalgia as a chronic disorder characterized by the presence of widespread pain accompanied by tenderness upon palpation of at least 11 of 18 predefined tender points throughout the musculoskeletal system [1]. In actual clinical practice it is currently common knowledge that there is nothing particularly sacred about the number 11. A patient with eight or nine tender points may have a clinical presentation otherwise typical of (and presumably responsive to the same

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interventions as) fibromyalgia. The same may hold true of a patient with diffuse tenderness who suffers pain which falls short of the definition of "widespread" (e.g. a patient with pain in the neck, shoulders, arms and lower back, but with little pain in the lower limbs). Thus, the ACR classification criteria should be interpreted as just that – i.e. classification criteria appropriate for use in the context of research – not as diagnostic criteria for clinical use.

The concept of using tender points as the defining feature of fibromyalgia has drawn ongoing debate [5]. The tender points have been criticized due to the arbitrary nature of the 11 point cutoff, due to the possibility of patients learning to expect pain and thus causing overestimation of the true number of tender points, due to the lack of a clear association between tender points and the underlying pathophysiology of fibromyalgia and due to the close association between tender points and distress, which has led to characterization of tender points as a "sedimentation rate of distress" [6]. Table 1 presents some areas of ongoing debate regarding the use of tender points in the classification and diagnosis of fibromyalgia. Notwithstanding these reservations, a large body of research continues to utilize tender points for the research of fibromyalgia.

Pain and tenderness are thus the defining features of the fibromyalgia syndrome. This central feature is currently attributed to an increase in central pain processing, i.e. to a disturbance in the way the central nervous system, including both the spinal cord and cerebral cortex, handles, transmits and processes pain. Allodynia, i.e. the perception of pain upon what would usually be an innocuous stimulation of the skin, is frequently present. The severity of pain may vary between patients as well as fluctuate in a particular patient at different points in time.

Although pain is the central feature of fibromyalgia, a constellation of additional symptoms are very frequently present as well (Table 2). Sleep disturbances are almost universal, patients describing frequent nocturnal awakening, non refreshing sleep and worsening pain after sleep; clinical sleep symptoms have been correlated with specific patterns of sleep disruption such as alpha intrusion and phasic alpha sleep activity [7].

Not surprisingly, fatigue is also an almost universal accompanying feature; when this symptom is overwhelming and the muscular pain less prominent, a diagnosis of chronic fatigue syndrome may be considered.

Symptoms of irritable bowel syndrome (IBS), such as intermittent diarrhea/constipation, abdominal bloating and abdominal pain are often encountered among fibromyalgia patients and should be actively sought in such patients.

Table 1
Areas of ongoing debate regarding the utilization of tender points for the diagnosis and classification of fibromyalgia

Issue of debate	Reference
Strong association with distress	Wolf [6]
Patient expectation leads to overestimation	Clauw and Crofford [60]
Tender points may reflect areas of increased peripheral sensitization	Vierck [61]
The 11 point cutoff is arbitrary	Clauw and Crofford [60]

Table 2
Clinical features accompanying fibromyalgia

Disturbed sleep pattern
Chronic fatigue
Irritable bowel syndrome
Headaches
Temporo mandibular joint disorder (TMJD)
Pre-menstrual syndrome

3. Findings on physical examination

The classical tender points of fibromyalgia are distributed symmetrically over the occipital, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteus, greater trochanter and at the medial fat pad of the knee. Each point is palpated with the thumb of the examiner, using gradually increasing pressure until the patient reports the pressure to be painful. A point is considered "positive" if less than 4 kg of pressure is required in order to evoke tenderness by this procedure.

The remainder of the physical examination of patients with fibromyalgia is typically within normal limits. No evidence of synovitis and no limitation of range of motion are expected, unless concomitant pathology exists. Similarly no objective evidence of muscular weakness is anticipated.

4. Laboratory evaluation

A laboratory workup is warranted in the evaluation of fibromyalgia mainly for exclusion of alternative differential diagnoses, as there are no specific laboratory findings typical of fibromyalgia. Inflammatory indices such as Erythrocyte sedimentation rate (ESR) and CRP are expected to be normal, although fibromyalgia should not be ruled out merely on the basis of an accelerated ESR, which is not uncommon among elderly patients. Rheumatoid factor and anti nuclear antibodies (ANA) are typically negative and are not warranted as screening tests, although the occurrence of an incidental positive result on these tests is not uncommon, increases with age, and hence should not be considered to rule out fibromyalgia. Thyroid dysfunction should be ruled out by appropriate screening and hyperparathyroidism, a condition classically associated with widespread pain, should be considered in the appropriate clinical setting.

Virological serologic tests are not routinely indicated and should be considered only when the clinical presentation is suggestive of active infection such as in the presence of prolonged fever and/or tonsilar exudation. Lyme disease serology is similarly not routinely indicated.

Table 3 lists common laboratory tests warranted in the routine evaluation of a patient suspected of suffering from fibromyalgia.

5. Pathogenesis of fibromyalgia

Significant progress has been made over the last decades regarding the pathogenesis of fibromyalgia. In the remainder of this review we shall briefly cover the various components

of our current understanding regarding the pathogenesis of fibromyalgia and will focus our discussion on the genetic basis of that syndrome.

5.1. Infection and vaccination

Various infectious agents have been linked to the development of fibromyalgia as well as to that of the closely related chronic fatigue syndrome (CFS). Viral agents, including hepatitis C [8], HIV [9] and hepatitis B [10] have been associated with fibromyalgia on epidemiological and clinical grounds. Lyme disease, a spirochetal disorder, carries several manifestations such as prolonged fatigue, arthralgia, difficulty with memory and concentration etc. which have drawn considerable attention to the possibility of chronic lyme disease as an entity overlapping with fibromyalgia and chronic fatigue [11]. Further research however has challenged this association [12] and antibiotic treatment of patients with a clinical presentation of fibromyalgia and a positive serological test for lyme disease does not seem to be warranted.

Parvovirus B19, once linked to the pathogenesis of fibromyalgia [13], has subsequently been shown not to be associated either with chronic fatigue syndrome or fibromyalgia [14]. Recently, we have reviewed the current evidence regarding the association between fibromyalgia and infection [15].

Secondary fibromyalgia is a term utilized in clinical practice to describe one of two different situations. In common practice clinicians use the term in order to describe patients in whom symptoms of fibromyalgia appear to develop on top of another (usually inflammatory) disorder, either of rheumatological character or otherwise. Rheumatoid arthritis [16], SLE [17], Sjogren disease [18] as well as IBD [19] have all been associated with a high prevalence of fibromyalgia. In such cases, it is important for the physician to recognize that a large part of the patient's suffering may be attributable to fibromyalgia rather than to the underlying disorder, a recognition which has significant clinical implications. In a more strict sense secondary fibromyalgia refers to the situation in which a localized painful condition such as tendonitis, herniated disc, etc. causes chronic pain, which over time appears to spread throughout the musculoskeletal system, thus evolving into fibromyalgia. In this chain of events it seems logical to assume that tonic painful input to the central nervous system plays a role in igniting the heightened pain processing characteristic of fibromyalgia.

Various forms of physical trauma have been implicated as triggering events in the pathogenesis of fibromyalgia; many patients will report the initiation or exacerbation of their symptoms following a traumatic event such as a whiplash injury. Increased rates of fibromyalgia have been demonstrated among patients undergoing cervical trauma during motor vehicle accidents [20] although this association has subsequently been challenged [21]. Most recently, Wynne-Jones et al., who found a 7.8% frequency of widespread pain within 12 months among a cohort of patients who underwent a motor vehicle collision, identified specific risk factors (e.g. post-collision physical symptoms, pre-collision health-seeking behavior, pre-collision somatization, perceived initial injury severity and older age) as predictors of onset of widespread pain following motor vehicle collision [22].

Table 3
Laboratory tests warranted in the initial evaluation of a patient suspected of suffering from fibromyalgia

Complete blood count
Renal function test, liver enzymes
ESR, CRP
TSH
Serum calcium, PTH, rheumatoid factor, EBV, CMV, HIV[a]

[a] Based on clinical consideration.

5.2. The role of biological amines/neurotransmitters in fibromyalgia

Our current understanding regarding the pathogenesis of fibromyalgia, as well as the therapeutic targets towards which many medications utilized in the treatment of fibromyalgia are aimed, owe much to pioneering research analyzing levels of serotonin and additional neurotransmitters in the central nervous system of fibromyalgia patients. Russel et al. classically demonstrated that both serotonin and norepinephrine were decreased in levels in the CSF of fibromyalgia patients [23]. On the other hand substance P, a biological amine known to correlate with pain, was found to be increased in level [24]. The CSF levels of the excitatory amino acid neurotransmitters aspartate and glutamate, which are involved in pain transmission through the spinal cord, have been shown to correlate with levels of pain in patients with fibromyalgia, although absolute levels were normal [25].

Although fibromyalgia is not considered an inflammatory disorder, the complex interaction between the biology of pain and inflammation has led to a considerable amount of research targeted at identifying alterations in levels of various cytokines in fibromyalgia patients. Levels of interleukin-1 receptor antibody (IL-1Ra) and IL-6 have been shown to be elevated in peripheral macrophages of fibromyalgia patients [26] while inflammatory cytokines such as IL1-beta, IL-6 and tumor necrosis factor alpha (TNFα) have been detected in skin biopsies taken from fibromyalgia patients, possibly indicating an element of neurogenic inflammation [27].

Thus, although it is not currently possible to determine with certainty which changes are primary and which may represent epiphenomena, an imbalance in CNS levels of a number of neurotransmitters, as well as in the level of various cytokines, appears to play a role in the pathogenesis of fibromyalgia.

6. Hormonal imbalance

As fibromyalgia has been closely linked to various forms of stress, and since a major pathway involved in the body's reaction to stress involves the activity of the Hypothalamic–Pituitary–Adrenal (HPA) axis, searching for alterations in this system in fibromyalgia appears to be a likely goal. Perturbations in the HPA axis have been demonstrated in fibromyalgia

patients [28]. Similarly, alterations in the functioning of the sympathetic nervous system, another closely related system involved in the response to stress, have frequently been described in fibromyalgia [29].

Despite the overwhelmingly higher prevalence of fibromyalgia among women compared with men, levels of sex hormones have not been clearly shown to differ between female fibromyalgia patients and controls, and thus the role of these hormones in the pathogenesis of fibromyalgia is not established [30].

7. Fibromyalgia and the concept of central sensitization

Central sensitization is an emerging biopsychosocial concept currently considered to characterize a wide spectrum of interrelated ''functional'' disorders, which may subsequently be better defined as central sensitivity syndromes [31]. Central sensitization constitutes a condition of general over reactivity of the central nervous system to a wide spectrum of stimulation. Clinical correlates which are particularly significant to the fibromyalgia syndrome include the phenomenon of allodynia, in which a normally un-painful stimulus is perceived of as painful and hyperalgesia, in which a normally painful stimulus is perceived of as more painful than expected. Additionally, central sensitization invokes prolonged electrophysiological discharge in response to stimulation as well as exaggerated response to various forms of stimulation such as noise, smell and chemical exposure. Various areas in the central nervous system are responsible for inhibiting ascending pain transmission within the spinal cord (e.g. the locus ceruleus, cortico-reticular system, brain stem and hypothalamus) through the activity of inhibitory neurotransmitters which include serotonin, norepinephrine, enkephalins, γ-amino-butyric acid (GABA), and adenosine [32]. A decrease in this pain inhibitory loop is an important component of the central sensitization syndrome [33]. Separate areas of the central nervous system including the limbic system and the medial thalamic nuclei, are involved in the affective response of the central nervous system to pain [34].

The advent of imaging techniques capable of providing real time information regarding the way specific areas within the central nervous system react to painful (as well as non-painful stimulation) has provided valuable insight into the biological meaning of central sensitization in fibromyalgia. Thus, using functional MRI (fMRI), Gracely et al. were able to demonstrate that conditions which resulted in comparable subjective sensation of pain, resulted in activation patterns that were similar in fibromyalgia patients and controls; on the other hand, similar levels of pressure (which invoke higher levels of pain among fibromyalgia patients relative to controls) resulted in activation of different areas and caused greater effects in patients [35]. Similarly Cook et al. showed that in response to painful stimuli, fibromyalgia patients had greater activity in the contralateral insular cortex than healthy controls, as demonstrated by fMRI [36].Thus, functional brain imaging such as fMRI has supplied fibromyalgia researches with a long-awaited tool for objective evaluation of pain. This tool enables further evaluation of various factors capable of influencing the functioning of the nervous system in fibromyalgia, ranging from pharmacological intervention to the presence of a significant other during testing.

8. From familial aggregation to genetic clues

It is currently well established that familial aggregation is characteristic of Fibromyalgia. Arnold et al. [37] studied 533 relatives of 78 probands with fibromyalgia as well as 272 relatives of 40 probands with rheumatoid arthritis. Fibromyalgia aggregated strongly in families: the odds ratio for fibromyalgia in a relative of a fibromyalgia proband versus fibromyalgia in a relative of a rheumatoid arthritis proband was 8.5. The number of tender points was also significantly higher in relatives of fibromyalgia patients when compared to relatives of patients suffering from rheumatoid arthritis.

Fibromyalgia has been described and investigated among various ethnic groups; Farooqi and Gibson have described fibromyalgia and soft tissue rheumatism as particularly prevalent among rural (compared with urban) inhabitants of northern Pakistan [38]. In a rural population in Western India, 5.5% of the population were found to suffer from ''soft tissue rheumatism'' (a term often overlapping with fibromyalgia) [39]; in Bangladesh fibromyalgia was described among 4.4% of individuals in a rural setting, 2.0% of patients in an ''urban slum'' and 2.3% of individuals in an affluent urban area [40]. Thus, fibromyalgia is by no means limited to Western (or Caucasian) populations and is found both in rural and urban settings.

As with other complex and multifactorial syndromes, the occurrence of familial aggregation in the case of fibromyalgia does not necessarily imply a genetic basis. Shared environmental factors are an equally valid target of investigation. Shared intrauterine influences affecting pain perception years after birth are another fascinating possibility [41].

Learned patterns of behavior may also evolve within families, influencing the way individuals react to stress and anxiety. Most intriguingly, an interaction has been identified between stressful life events and genetic predisposition to the development of depression, another affective spectrum disorder [42]. Similar interactions could be operational in fibromyalgia. Notwithstanding all these (possibly complimentary) possibilities, genetic factors are currently considered likely culprits in the etiology of fibromyalgia. The remainder of this review will focus on the various genetic candidates which have been studied in the pathogenesis of fibromyalgia.

8.1. Fibromyalgia candidate genes

Early research into the genetic basis of fibromyalgia was directed towards the possibility of linkage to the HLA antigens. One such early study [43], conducted before the establishment of the current ACR fibromyalgia criteria, found high levels of the DR4 antigen − 64% versus 30% among healthy controls. A subsequent sibship study [44] described significant linkage of fibromyalgia to the HLA region. Taken together these results imply that HLA linkage may be a marker to some as

yet unidentified genetic marker of fibromyalgia. Other studies however failed to support the association between fibromyalgia and the HLA antigens [45].

9. Candidate genes involved in the metabolism of serotonin

In view of the evidence regarding alterations of the serotoninergic system in the pathogenesis of fibromyalgia [23] genetic research was initially directed towards genes involved in modulation of that system. Offenbaecher et al. [46] compared the genotype of the serotonin transporter gene (5-HTT) promoter region in fibromyalgia patients with healthy controls. An increased frequency of the S/S genotype of the 5-HTT gene was demonstrated among patients versus controls.

These results were subsequently confirmed by a study analyzing Palestinian Arabs and Israeli Jews [47].On the other hand, another study directed at the T102C polymorphism of the 5-HT2A-receptor gene [48], another serotonin receptor candidate gene, failed to demonstrate a difference in the frequency of the polymorphism among fibromyalgia patients and controls.

Similarly, a study focusing on the serotonin receptor subunit genes, HTR3A and HTR3B [49] found no significant difference in these genes among fibromyalgia patients.

10. Dopamine receptors in fibromyalgia

Dopamine is a crucial CNS neurotransmitter involved in multiple activities including pain transmission. Alterations in dopamine metabolism are involved in many disturbances of the CNS including Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder [50]. Pramipexole, a dopamine-3 agonist has been tested in the treatment of fibromyalgia [51].In addition, fibromyalgia has been linked with reduced presynaptic dopamine activity demonstrated on positron emission tomography [52].In view of these clues, genetic markers linked to the dopaminergic system have been another area of interest in fibromyalgia research. Thus, Increased sensitivity or density of dopamine D2 receptors has been demonstrated in fibromyalgia patients [53]. Similarly, polymorphisms affecting the number of repeats in the third cytoplasmic loop of the D4 receptor gene have been shown to be significantly decreased in frequency in fibromyalgia patients [54].

Intriguingly, an association has been described between Post Traumatic Stress Disorder (PTSD) a syndrome which carries surprising clinical and epidemiological similarity with fibromyalgia [55] and a dopamine transporter SLC6A3 3′ variable number tandem repeat (VNTR) polymorphism [56]. Whether similar associations between fibromyalgia and the dopamine transporter gene exist is currently unknown.

11. Studies of the catechol-*O*-methyl transferase gene polymorphism in fibromyalgia

3-Methoxy-4-hydroxyphenethylene (MPHG), which is a major metabolite of norepinephrine, has been found to be decreased in the cerebrospinal fluid of fibromyalgia patients [23]. Since norepinephrine is considered to play an important role in spinal inhibition of pain transmission, this finding may imply a reduction in this crucial aspect of pain modulation in fibromyalgia. Thus, attempts have been made to study genetic markers involved in metabolism of catecholamines. One such major enzyme is catechol-*O*-methyl transferase (COMT). In a study of three COMT gene polymorphisms – LL, LH and HH – in fibromyalgia patients and healthy controls [57] the combination of LH and LL genotypes occurred more often in patients compared to controls, whereas the HH genotype was less frequent among patients compared to controls. This finding may bear relevance both for the pathogenesis of fibromyalgia as well as for the pharmacogenetic response of the patients to treatment with medications which act through adrenergic pathways.

12. Substance P in fibromyalgia

Substance P is an 11-amino-acid peptide neurokinin, with diverse functions in nociception [58]. As substance P has been clearly shown to be elevated in level in the CSF of fibromyalgia patients [24], an attempt has been made to find an association between the tachykinin NK1 substance P receptor and fibromyalgia. A trend towards an increase frequency of the G>C substitution at position 1354 in the 3′ untranslated region of the NK1 receptor was identified, which did not however reach statistical significance [59]. Further research may shed more light on the possible role of substance P receptors in fibromyalgia and in associated disorders.

13. Conclusion

Fibromyalgia is a common, frustrating disorder characterized by widespread musculoskeletal pain. It frustrates physicians, due to the vagueness of the complaints, the lack of clear laboratory and imaging findings and the intransigence to treatment; it frustrates patients to a much greater degree due to the severity of the suffering, the lack of specific treatment and in many cases – the disbelief and skepticism handed out by health care professionals as well as others. As our understanding of the biological basis in general and the genetic underpinning in particular of fibromyalgia increases, we hope to gain a better understanding of the true nature of the disorder, attain more rational therapeutic modalities and help patients. In the mean time though, since we are bound to encounter fibromyalgia patients frequently, it is our primary responsibility to attain an updated and practical understanding of the syndrome, to be acquainted with the therapeutic modalities available and last but not least – to offer our patients the empathy and trust they so urgently seek.

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