Fibromyalgia, Fatigue, and Headache Disorders

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Fibromyalgia, chronic fatigue, and primary headaches are common and debilitating disorders, and their related symptoms of widespread pain, fatigue, and headache have complex interactions and different implications for classification, diagnosis, mechanisms, and treatment. The "continuum" or "spectrum" idea and the modular headache theory are fundamental concepts in understanding these interactions. The overlap between symptom-based conditions leads the reasons to consider them as "functional somatic syndromes." Management of these patients includes a correct diagnosis, appropriate investigation for associated conditions, adequate treatment, and considering the therapeutic opportunities and limitations the comorbid disorders may impose.

Introduction

Fibromyalgia, chronic fatigue, and headaches are very common and debilitating conditions [1]. They are linked in several complex ways. Headache is part of the chronic fatigue syndrome [2] and often complained of by fibromyalgia patients [3]. Fatigue is often reported in both fibromyalgia and headache patients [4,5•], and fibromyalgia is common in migraine patients and greatly overlaps with chronic fatigue syndrome [6•,7]. Fibromyalgia, chronic fatigue syndrome, and primary headaches are symptom-based disorders. They may be different spectra of the same disorder, or, in fact, separate entities. Despite the amount of suffering and disability they cause, little is known about their relationship. Their subjective nature and prior lack of definition make them difficult to study, and are probably the cause of paucity of research in the area. In order to clarify this obscure issue, separate topics are discussed in this article, including definition, epidemiology, comorbidity, mechanisms, treatment, and implications for future researchers.

Definition

The first step into the study of a complex scenario is to establish a solid, valid definition. For clinical practice and epidemiologic research, it is important to have precise definitions to enable reliable and valid diagnosis. Because there is no true diagnostic gold standard for fibromyalgia, fatigue, and the primary headache disorders, it is difficult to study validity. It is difficult to define diagnostic boundaries for symptom-based conditions. It is important to consider and define widespread pain as the cardinal feature in fibromyalgia, fatigue in chronic fatigue syndrome, and headache in primary headache disorders, including migraine. The ideas and discussion in this article regarding epidemiology, mechanisms, and treatment may interchange from the symptoms to their respective disorders.

Classification and Diagnostic Criteria

Despite its impact and relevance in both clinical practice and general population, headache disorders, fatigue, and fibromyalgia have been better defined and studied only in the past decade. The International Headache Society (IHS) classification and diagnostic criteria were published in 1988 [8]; nevertheless, one of the most important conditions, chronic migraine, is not part of the current classification, and its criteria were proposed by Silberstein *et al.* [9] in 1996 (Table 1). The American College of Rheumatology diagnostic criteria for fibromyalgia was published in 1990 (Table 2) [10]. An attempt at standardization of chronic fatigue syndrome diagnostic criteria was made by the Centers for Disease Control (CDC) in 1988 [11], and a simplified definition was also proposed in 1994 (Table 3) [13]. The understanding of each condition is growing, but many areas of uncertainty are still present.

Between fibromyalgia, fatigue, and headache, the latter is the easiest to define. Headache is defined as pain localized in the occipital, parietal, temporal, or frontal regions of the head; it occurs in one, some, or all regions; and it is one sided or bilateral. It can be episodic or chronic, intermittent, or continuous. Headache is usually associated with many symptoms, including nausea, vomiting, phonophobia, photophobia, visual phenomena, and autonomic features. Headache is one of the most common complaints encountered by the practicing physician. Headaches can be either primary or secondary. Primary headache disorders,

Table 1. Proposed diagnostic criteria for chronic migraine (transformed migraine)

A) Daily or almost daily (>15 d/mo) head pain for >1 month
B) Average headache duration of >4 h/d (if untreated)
C) At least one of the following:
  1. History of episodic migraine meeting any IHS criteria 1.1 to 1.6
  2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
  3. Current headache meets IHS criteria for migraine 1.1 to 1.6 other than duration.
D) At least one of the following:
  1. There is no suggestion of one of the disorders listed in group 5-11
  2. Such disorder is suggested, but it is ruled out by appropriate investigations
  3. Such disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder

IHS—International Headache Society.
Adapted from Silberstein *et al.* [9].

Table 2. American College of Rheumatology diagnostic criteria for fibromyalgia*

1) History of widespread pain:
Pain on both sides of the body, both above and below the waist.
Axial skeletal pain must also be present (cervical spine, anterior chest, thoracic spine, or low back).
This must have been present for at least 3 months
2) Tender point pain
On digital palpation using a force of 4 kg
Must be present in 11 of 18 paired bilateral tender point sites
Occiput: bilateral, at the suboccipital muscle insertions
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
Trapezius: bilateral, at the midpoint of the upper border
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
Second rib: bilateral
Lateral epicondyle: bilateral
Gluteal: bilateral, in upper outer quadrants of buttock in anterior fold of muscle
Greater trochanter: bilateral, posterior to the trochanteric prominence
Knee: bilateral, at the medial fat pad proximal to the joint line

*For a diagnosis of fibromyalgia, both criteria must be positive. The presence of a second disorder does not exclude the diagnosis of fibromyalgia.
Adapted from Wolfe *et al.* [10].

particularly migraine, are better understood, but secondary headache disorders are also studied [12].

Fibromyalgia is defined as a painful, nonarticular condition predominantly involving muscles, and it is recognized as the most common cause of chronic, widespread musculoskeletal pain. In 1990, The American College of Rheumatology standardized a starting point to the study of patients with this condition [10]. The diagnostic criteria include the presence of widespread pain (defined as pain in the left and right sides of the body as well as both above and below the waist) for at least 3 months. Axial skeletal pain, defined as pain in the cervical spine, anterior chest, thoracic spine, or low back, must also be present. In addition, the patients must report pain in at least 11 of 18 tender point sites (Table 2, Fig. 1).

Fatigue is a universal symptom experienced by the human being. As headaches, fatigue can be primary (in chronic fatigue syndrome), or secondary, as a symptom of many disorders including cancer [13], HIV [14], fibromyalgia [15], depression [16], sleep apnea [17], multiple sclerosis [18], or systemic lupus erythematosus [19]. In clinical practice, terms such as sleepiness, tiredness, generalized weakness, loss of strength, and loss of interest are often confused and used to represent fatigue. In an attempt to increase clarity, fatigue has been separated into different subtypes. Chalder *et al.* [20] provided two different domains (mental and physical fatigue) in a fatigue scale. Morriss *et al.* [21] analyzed four aspects of fatigue: 1) cognitive difficulties, 2) tiredness and sleepiness, 3) strength and endurance, and 4) loss of interest and motivation.

Chronic fatigue syndrome is defined as a sufficiently severe fatigue of new onset that persists or relapses for more than 6 months, is not substantially alleviated by rest, and results in reduction in previous levels of occupational, educational, social, and personal activities.

The "Spectrum" or "Continuum" Concept

For primary headaches, the most important and difficult boundary is the one between migraine and tension-type headache. Although some view these disorders as distinct entities, others favor the "spectrum" or "continuum" concept, the idea that migraine and tension-type headache exist as polar ends on a continuum of severity, varying more in degree than in kind. Lipton *et al.* [22•], in the Spectrum study, found that migrainous and tension-type headaches in migraine patients responded to sumatriptan, giving more support to the spectrum theory. In addition, in the early phase of a migraine headache, the patient may have mild, nonpulsating pain and a lack of nausea, vomiting, photophobia, and phonophobia, in which case the headache resembles a tension-type headache.

Modular Headache Theory

Young *et al.* [23•] recently published the modular headache theory, a comprehensive approach to better understand symptoms in primary headache disorders. A module is a group or network of neurons within the brain, blood vessels, and possibly other organs that produces a feature or symptom of headache. Some of the proposed modules are throbbing vascular pain, cervical tenderness, nausea and vomiting, photophobia and phonophobia, autonomic

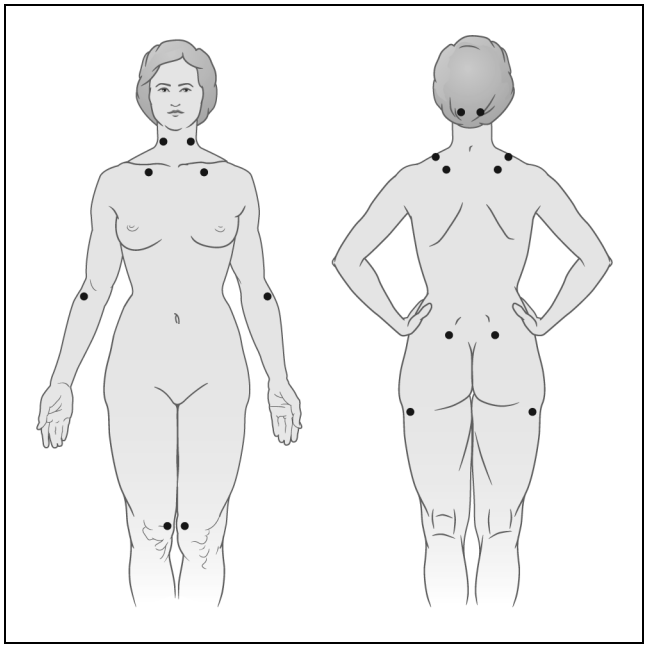

Figure 1. Tender points for fibromyalgia.

symptoms, aura, prodrome, and circadian and circannual variation. The same theory can be expanded to the analysis of widespread pain and fatigue in headache patients. Considering them as other modules helps clarify the issue. The idea of accepting modules to occur randomly or in certain associations in primary headaches, without imposing preexisting biases, explains associations of primary headaches, mixed headaches, and other symptoms such as widespread pain (fibromyalgia) and fatigue in headache patients.

Epidemiology

Migraine is a very common condition worldwide. Estimates of its prevalence have varied widely, ranging from 3% to about 35%. The differences can be accounted for by the differing definitions and methodologies employed. A reasonable estimate of 1-year prevalence of migraine in adults is 10% to 12% (6% in men and 15% to 18% in women). Using the IHS criteria, Rasmussen *et al*. [24] examined the population distribution of all headache disorders via in-person clinical assessment in a large, representative community sample in the greater Copenhagen area. The lifetime prevalence of tension-type headache was 78% and migraine was 16%.

The prevalence of chronic daily headache in the general population is 4% to 5%, and the prevalence of chronic migraine (transformed migraine) is 2% to 4% [25].

The estimated prevalence of fibromyalgia in the general population is 2%, (3.4% in women and 0.5% in men). It increases with age, reaching 7% in women aged 60 to 80 years [26]. It is reported to be 5.7% in a general medical clinic [27]. It was found at a prevalence of 14% [28] and 20% [29] in rheumatology clinics. Despite its prevalence and specific criteria for diagnosis, the average patient with fibromyalgia has seen more than five physicians, spent thousands of dollars, and had symptoms for 5 years before an accurate diagnosis is made [30].

Table 3. Centers for Disease Control diagnostic criteria for chronic fatigue syndrome

1) Clinically evaluated, medically unexplained fatigue of at least 6 months duration that is:
Of new onset
Not a result of ongoing exertion
Not substantially alleviated by rest
A substantial reduction in previous levels of activity
2) The occurrence of 4 or more of the following symptoms:
Subjective memory impairment
Tender lymph nodes
Muscle pain
Joint pain
Headache
Unrefreshed sleep
Post-exertional malaise (>24 h)

Adapted from Fukuda *et al.* [11].

Although fatigue is a human experience and many people report experiencing chronic fatigue intermittently, chronic fatigue syndrome is different and less common. The prevalence of fatigue varies and depends on its case definition and the population studied. The lifetime prevalence of chronic fatigue was 33% in women and 21% in men [31]. In a community-based study in the greater Seattle area, the estimated prevalence of chronic fatigue syndrome was 0.2%, and the prevalence of chronic fatigue alone was 1.8% to 6.3% [32].

Little is known about the epidemiology of fibromyalgia, fatigue, and headaches and their relationship in the general population.

Comorbidity

Feinstein [33] coined the term "comorbidity" originally with reference to coexistent conditions in clinical trials. However, comorbidity is currently defined as an association between two disorders that is more than coincidental [34].

Comorbidity in chronic diseases is important from a number of different perspectives, including classification, diagnosis, mechanisms, and treatment. Co-occurrence of diseases can complicate diagnosis, as a high degree of symptomatic overlap occurs among the conditions associated. Questions regarding classification may arise, for example, in a patient presenting with chronic widespread pain, a migrainous headache, and fatigue. Should the patient be classified as having three different disorders (fibromyalgia, migraine, and chronic fatigue syndrome)? Should the patient be diagnosed with migraine and associated widespread pain and fatigue, fibromyalgia with headache and fatigue, or chronic fatigue syndrome with

widespread pain and headache? Is it worthwhile including chronic fatigue and fibromyalgia in the IHS classification as chronic migraine subtypes, as acute medication overuse is? Management of this type of patient is also an important issue. How should this patient be treated? Does it make any difference diagnosing these associated conditions?

Patients seek help from doctors for symptoms and doctors diagnose diseases to explain them. Symptoms are the patient's subjective experience of changes in his or her body. Diseases are objectively observable abnormalities in the body. Difficulties arise when the doctor can find no objective changes to explain the patient's subjective experience.

Symptom-based diseases are always subjective in nature. It is proposed that they should be grouped as functional somatic syndromes [35]. Wessely *et al*. [36] postulated that the existence of specific somatic syndromes is largely an artefact of medical specialization: irritable bowel syndrome is seen by the gastroenterologist, fibromyalgia by the rheumatologist, migraine by the neurologist, premenstrual syndrome and chronic pelvic pain by the gynecologist, atypical chest pain by the cardiologist, chronic (post-viral) fatigue syndrome by the infectologist, and anxiety and depression by the psychiatrist.

The rationale for considering these syndromes in a broader perspective and grouping them as functional somatic syndromes is that 1) there is overlap in case definition of specific syndromes (*eg*, headache and widespread pain is part of the CDC criteria [11] for chronic fatigue syndrome); 2) patients with one functional syndrome frequently meet diagnostic criteria for other syndromes [37]; 3) patients with different functional syndromes share nonsymptom characteristics, including female preponderance, current and past episodes of anxiety and depression, evidence of abnormalities in serotonin pathways, history of childhood maltreatment and abuse, and difficulties in doctor-patient relationship [38]; and 4) all functional syndromes respond to similar therapies, such as antidepressants and psychologic therapies [7].

The problem with comorbidity is not limited to differential diagnosis. When comorbid diseases occur, the challenge is to recognize that more than one disease may be present. Migraine is unrecognized and under-treated [39] as fibromyalgia [30] and chronic fatigue [32]. The overlap between fibromyalgia, fatigue, and headache is considerable [40]. The association of these disorders may increase the extent that they are under-diagnosed and undertreated. Time constraint and lack of medical education are barriers to the diagnosis of these conditions.

A headache specialist or a neurologist may under-diagnose fibromyalgia and chronic fatigue in headache patients; however, there is no data on the extent of this problem. It is easy for those specialists to assume widespread pain and fatigue as neurologic symptoms related to migraine, explaining them as part of the migraine pathophysiology and clinical picture, but it lacks confirmation and may be a dangerous simplification. This may also be an important issue for rheumatologists, primary care physicians, and other specialists dealing with the fibromyalgia, fatigue, and headache association.

When illnesses are comorbid, the principle of parsimony does not apply; the presence of migraine should increase, not reduce, the suspicion that other disorders may be present.

It is unknown whether the presence of fatigue or widespread pain is more likely to occur in primary or secondary headache disorders, in migraine or tension-type headache, or in association of other symptoms or modules (nausea, vomiting, photophobia, phonophobia, aura) [23•]. The biologic basis and natural history of these symptoms/disorders have yet to be determined in headache patients

Other diseases may cause or worsen both headache, widespread pain, and fatigue, such as hypothyroidism, sleep disorders (*eg*, sleep apnea and insomnia), multiple sclerosis, infections (*eg*, HIV and viral infections), post-traumatic syndrome, (Magnusson) depression, and anxiety.

Comorbidity has important implications for treatment. A comorbid illness provides therapeutic opportunities but also imposes therapeutic limitations. In certain instances, two or more conditions may be treated with a single drug. Tricyclic antidepressants can be used in migraine prevention and fibromyalgia. Conversely, in individuals with more than one disease, drug categories may be contraindicated (*eg*, β-blockers can aggravate or induce fatigue in migraine patients).

Headache in Fibromyalgia

Nicolodi *et al*. [41] studied 89 fibromyalgia patients and stated "fibromyalgia sufferers are headache sufferers." All patients had a headache diagnosis (84 migraine, 5 tension-type headache).

Burg [42] studied 25 patients with fibromyalgia. The majority of patients were women, and 80% presented with depression, anxiety, and sleep disorder. Most of the patients had this condition for greater than 6 months, and all but a few had headaches. Back pain, diffuse tender trigger points, irritable bowel symptoms, and dysmenorrhea were also common.

Hudson *et al*. [43] evaluated 33 women with fibromyalgia for concomitant medical and psychiatric disorders. These patients were found to have high lifetime rates of migraine, irritable bowel syndrome, chronic fatigue syndrome, major depression, and panic disorder. They also exhibited high rates of familial major mood disorder. More studies on headache characteristics, diagnosis, impact, and management in fibromyalgia patients are necessary.

Headache in Chronic Fatigue

In an examination of the working case definition of chronic fatigue syndrome, Komaroff *et al*. [44] studied 369 patients with debilitating fatigue compared with 311

healthy subjects. Headaches were reported in 59% of patients with chronic fatigue and only by 7% of healthy control patients. Nausea was reported in 58% of patients compared with 3% of control patients; however, it is unclear whether nausea was associated with headache. Other headache features were not examined (photophobia, phonophobia, pain quality, unilaterality, frequency, duration) and migraine or tension-type headache diagnostic criteria were not applied.

In studies focusing on fatigue in other diseases (*eg*, sleep apnea, multiple sclerosis, and HIV), the relationship of headache and fatigue was not established.

Fibromyalgia in Headache/Migraine

Paiva *et al*. [45] studied 25 patients with various headache diagnoses but a common clinical feature: all patients reported morning or nocturnal headaches. Fibromyalgia was diagnosed in 24% of patients according to the presence of alpha-delta in slow wave sleep in polysomnography and then confirmed by a rheumatologist applying the diagnostic criteria for fibromyalgia of the American College of Rheumatology [10].

Nicolodi *et al*. [41] studied 205 severe headache sufferers (164 migraine, 41 tension-type headache). Forty-eight percent (69 migraine, 30 tension-type headache patients) were diagnosed with fibromyalgia. Fibromyalgia also improved with headache treatment. They discuss "central panalgia," a term coined by Sicuteri in 1971 to describe a syndrome involving systemic pain. It is argued that this syndrome is identical with fibromyalgia and arises from a defective pain-suppressing system. Further arguments were proposed to support the recognition of two different types of central panalgia: the somatogenic and the viscerogenic; however, no further studies explored this issue.

Peres *et al*. [6•] recently studied 101 chronic migraine patients and diagnosed fibromyalgia according to the American College of Rheumatology diagnostic criteria [10] in 35% of patients. Beck depression inventory was applied and a diagnostic criteria for insomnia proposed. Patients with fibromyalgia had more insomnia, were older, and their headaches were more incapacitating than patients without fibromyalgia. Insomnia and depression predicted fibromyalgia in chronic migraine patients. A subtype of chronic migraine patient, one with fibromyalgia, depression, and insomnia, comprised 25% of the sample; this population may be a subtype of chronic migraine (Fig. 2).

Fatigue in Migraine

Fatigue is a common symptom reported by migraine patients. Spierings and van Hoof [46] found complaints of fatigue in 70% of headache patients, and they rated the intensity of their fatigue significantly higher than control subjects. They also found headache patients slept significantly shorter and took longer to fall asleep. Solomon *et al*. [47] found 52% of patients with fatigue were associated with chronic daily headaches. Henry *et al*. [48] found physical or mental fatigue as a precipitating factor in 46% of migraine patients in the general population.

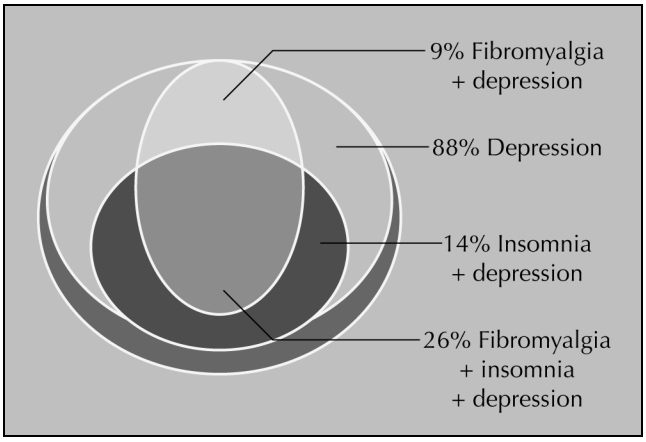

Figure 2. The Venn diagram shows the comorbidity of fibromyalgia, insomnia, and mild to severe depression in transformed migraine patients. All the patients diagnosed with fibromyalgia and the majority of patients with insomnia had mild to severe depression. Note that 26% of patients had depression, fibromyalgia, and insomnia (*center*). (*Adapted from* Peres *et al*. [6•].)

Peres *et al*. [5•] studied fatigue in chronic migraine patients. The Fatigue Severity Scale (FSS), the Chalder fatigue scale, the Beck depression inventory, and the state and trait anxiety questionnaire were applied. The CDC diagnostic criteria for chronic fatigue syndrome (CFS) were applied in all patients.

Eighty-four patients reported significantly disabling fatigue (FSS scores >27), and 66.7% patients met the CDC criteria for CFS. The CDC criteria were modified in order not to consider headache as part of it. Fifty percent of patients still fit the modified criteria for CFS. Depression and anxiety scores correlated with fatigue scores. Women had higher FSS scores than men, and physical fatigue was associated with fibromyalgia. This study shows fatigue in general is related to depression and anxiety in chronic migraine, and physical fatigue more related to fibromyalgia.

Mechanisms

The pathophysiology of fibromyalgia, chronic fatigue, and headaches is complex. They may share mechanisms; however, differences and similarities in diverse aspects have yet to be determined.

The mechanisms involved in fibromyalgia are altered neurotransmitters and pain-modulating neuropeptides (serotonin, substance P), and neuroendocrine changes (melatonin, hypothalamic-pituitary-adrenal axis). Genetic, immunologic, psychologic, and sleep abnormalities are also considered [15].

Peripheral and central mechanisms have been implicated in the pathophysiology of chronic fatigue. Hypotha-

lamic involvement is suggested by an impairment of central corticotropin-releasing hormone synthesis and release; altered serotoninergic, melatonin, and noradrenaline function have also been implicated. Cytokines may be involved; elevated levels of interleukin-1β (IL-1β) and IL-6 have been reported. The role of infections, specifically viruses, is uncertain in the etiology of chronic fatigue [49].

The possible mechanisms shared by fibromyalgia, fatigue, and headache disorders, particularly migraine, are dysfunction in serotoninergic neurotransmission, melatonin secretion, and immunologic factors. Central sensitization has recently been implicated in fibromyalgia [50] and migraine [51].

Management

The patient with headache, fatigue, and fibromyalgia is difficult to manage. First, a correct diagnosis has to be made according to diagnostic criteria for fibromyalgia [10], chronic fatigue syndrome [11], and primary headache disorders [8]. Differential diagnosis to be considered include thyroid dysfunction (hypothyroidism and hyperthyroidism), anemia, sleep disorders (sleep apnea and restless leg syndrome), infections (HIV, hepatitis, herpes, Epstein-Barr, cytomegalovirus, mycoplasma), and rheumatic syndromes (osteorthritis, rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatica, systemic lupus erythematosus, Sjogren's syndrome, polymiositis, and eosinophilia-myalgia syndrome). Evaluation of associated conditions is also important. Psychiatric disorders, including major depression, bipolar disorder, the anxiety spectrum disorders (generalized anxiety, phobias, panic disorders, mixed anxiety, and depressive disorder), and obsessive-compulsive disorder need to be evaluated. A personality disorder diagnosis may also be useful to assess. Other syndromes may coexist, such as irritable bowel syndrome and premenstrual dysphoric syndrome.

Assessing thyroid function, erythrocytes, leukocytes, antibodies, and inflammatory markers may be useful in the diagnosis. Polysomnogram may be indicated when sleep disorders are suspected. A lumbar puncture may disclose an increase in intracranial pressure (idiopathic intracranial hypertension) in patients with daily headaches. An increase in the body mass index and the presence of tinnitus increases the possibility of the diagnosis; however, one cannot exclude this possibility in patients without tinnitus and high body mass index.

Treatment may be variable and should be tailored to each patient. Therapy should include exercise, diet, good sleep hygiene, antidepressants, and other medications depending on the patient's presentation

There is a need for further studies for the better understanding of the fibromyalgia, chronic fatigue, and headache disorders relationship. Genetics, epidemiology and classification, pathophysiology, and treatment are areas for future development.

Conclusions

Widespread pain, fatigue, and headache are common and debilitating symptoms, and their related symptom-based disorders (*ie*, fibromyalgia, chronic fatigue, and primary headache disorders) have complex interactions and different implications for classification, diagnosis, mechanisms, and treatment. Further studies are necessary to clarify this important issue. These patients need careful management, including correct diagnosis, evaluation of associated conditions, and assessment of treatment implications that comorbid disorders may impose.

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