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PERSPECTIVE & COMMENTARY

Commentary

The Comorbidity of Fibromyalgia Syndrome and Attention Deficit and Hyperactivity Disorder from a Pathogenic Perspective

Introduction

Fibromyalgia

Fibromyalgia (FM) is a central pain sensitivity syndrome manifesting as widespread chronic pain and tenderness with no evidence of soft tissue inflammation. Central sensitization corresponds to heightened and long-lasting sensitivity to peripheral, sometimes subthreshold, noxious stimuli due to long-term potentiation of synapses and altered activity of monoaminergic neurotransmission systems within central pain pathways [1]. Clinical manifestations include widespread chronic pain, muscle tenderness, joint stiffness, fatigue, sleep disturbance, mood disturbance, and cognitive symptoms [1].

Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder beginning in childhood, classically manifesting as a triad of hyperactivity, impulsivity, and attention deficit, or any combination thereof. It is a highly heritable and multifactorial disorder presenting with both genetic and environmental determinants, as well as complex interplay between the two. Both determinants converge on downhill disturbances in the monoaminergic systems, mainly in the prefrontal cortex, manifesting as difficulties in executive (e.g., planning, response inhibition, working memory, and vigilance) and nonexecutive functions (e.g., timing, memory storage, reaction time) [2].

Adult ADHD

Ten percent to 30% of ADHD cases persist until adulthood but differ in presentation from that in children, with a decrease more important for hyperactivity symptoms—persisting sometimes as restlessness—than for inattentive symptoms, which constitute the major impact of the disorder. Furthermore, the male predominance seen in childhood markedly decreases with age [3]. The diagnosis of ADHD at an adult age is made difficult: first, by the requirement of an accurate retrospective report of childhood symptoms; second, by the frequent presence of one or more co-occurring psychiatric disorders; and third, by the not-so-seldom feigning of ADHD symptoms by some individuals to acquire stimulant prescriptions for nonmedical purposes [4].

Background of the Comorbidity of Fibromyalgia and Adult ADHD

The overlap between FM and adult ADHD is not incidental and deserves particular attention. Studies have indeed put forward that the prevalence of FM seems to be higher in adults with ADHD than in controls or even patients with cognitive complaints without ADHD. Inversely, adult ADHD seems to be more frequent in FM [5]. Chronic pain has in fact an interruptive effect on attention, and according to a study conducted by Moore et al. in 2012 [6], it preferentially affects complex attentional performances—attention span, attentional switching, and divided attention—as compared with simpler attentional tasks.

In the current issue, van Rensburg et al. present an article entitled “Screening for Adult ADHD in Patients with Fibromyalgia Syndrome,” in which they illustrate a high prevalence (44.72%) of adult ADHD in 123 previously confirmed FM patients, screened using the ADHD Self Report Scale v1.1. More importantly, they emphasize the under-recognized and disabling nature of cognitive complaints, sometimes surpassing that of chronic pain. In our manuscript, we comment on the study presented by van Rensburg et al. to better investigate the noteworthy comorbidity between FM and ADHD, where cognitive and pain tolerance alterations can be found, owing to the presence of shared neurobiological mechanisms, early life traumatic events, and emotional dysregulations in both disorders.

ADHD and Fibromyalgia Comorbidity

The medical literature has already looked at the comorbidity between ADHD and FM, with studies estimating that around 25% of FM patients have a dual diagnosis of adult ADHD [7]. No studies, however, have used the new modified American College of Rheumatology 2010

diagnostic criteria for FM, which, compared with the 1990 criteria, focus more on nonpainful symptoms, namely cognitive complaints. As such, the comorbidity may have very well been under-reported.

A study by Reyero et al. [8] in 2010 has shown that a history of childhood ADHD was more common in women with FM, and hence postulates that later FM cognitive symptoms may be the inattentive symptoms of childhood ADHD persisting through adult age. Furthermore, Kaplan et al. [9] present evidence that the increased rate of accidents found in chronic pain patients—and that often trigger the long-term potentiation process leading to increased pain sensitivity—may be the consequence of undiagnosed and untreated ADHD in childhood.

Moreover, the frequent comorbidity of FM and adult ADHD may have interesting therapeutic implications, as deficits in dopaminergic neurotransmission have been identified in both conditions. One example in FM is the decreased repetition of the Dopamine Receptor D4 (DRD4) gene, normally characterized by a highly polymorphic sevenfold repeat [10]. This seven-repeat variation is associated with thinner right orbitofrontal, inferior prefrontal, and posterior parietal cortices and has also been demonstrated in ADHD [11]. Stimulants such as methylphenidate, used in the treatment of ADHD, and dopamine agonists such as pramipexole have indeed been shown to significantly improve pain and other FM symptoms such as cognitive difficulties in several studies [12].

Crossover Symptoms

Cognitive Dysfunction in FM Patients

Cognitive complaints in patients with FM, such as slower reaction time, inability to inhibit irrelevant information, or difficulties dividing attention, are due to dysfunctions in the prefrontal cortex. Park et al. [13] showed that individuals with FM fared worse than age-matched controls and similarly to older controls on all cognitive tasks except speed of processing. This emphasizes that patients' subjective complaints should be taken seriously as their cognitive functions are clearly not age-appropriate (30). Furthermore, Park et al. showed that these cognitive impairments correlate with pain severity but not with depressive or anxiety symptoms, proving that they are indeed core symptoms of FM and not merely secondary to a comorbid condition. As such, comorbidities do worsen the cognitive profile of FM patients but do not explain the entirety of the deficits.

Pain in ADHD Adults

Data are scarce when it comes to the evaluation of pain in individuals with ADHD. In one interesting study, Treister et al. [14] found that adult ADHD patients had lower objectively measured pain threshold and tolerance time compared with the control group. In a study conducted by Stray et al. [15], adults with ADHD had more motor problems and higher muscle tone. Subsequently, they displayed significantly higher and more widespread pain, as a result of long-term motor restriction and heightened muscle tone.

The Neurobiology of FM and ADHD

Fibromyalgia

As shown in our previous paper [1], FM results from the interaction of several pathogenic mechanisms. First, there is an increase in the activity of the bottom-up excitatory pain pathways with an upsurge of such transmitters as substance-P, nitric oxide, nerve growth factor, and glutamate. Concomitantly, there is a decrease in the activity of the top-down inhibitory pathways and in the levels of dopamine, norepinephrine, serotonin, and endogenous opioids. The long-term consequence of this imbalance is a functional then structural central sensitization with subsequent widespread reduction in pain thresholds, increase in temporal summation, prolonged after-effects of noxious stimuli, and reduced overall pain tolerance. Alongside this, chronic sympathetic hyperactivity with hyporesponsiveness in acute stress settings acts to exacerbate symptoms of pain and fatigue. Furthermore, the hypothalamic–pituitary–adrenal axis also displays disturbances in terms of chronic hypoactivity, along with flattening of diurnal cortisolemia variations, which also participate in the development of symptoms of pain, fatigue, and depression. In this regard, central sensitization is now viewed as the cornerstone of the development of FM and is thought to be correlated with the burden of physical and psychological traumas experienced before disease onset that are impinged on the genetically determined defective neural circuitry responsible for the processing of these traumatic experiences. Peripheral pathogenic processes have also been studied, such as impairments in nociceptor sensitivity, immunologic alterations, and local metabolic mechanisms within the muscles (i.e., ATP depletion, lactic acid accumulation, hypocarbia) [1].

Attention Deficit Hyperactivity Disorder

ADHD is characterized by several functional and structural anomalies in various cerebral pathways, notably the fronto–striatal, fronto–parieto–temporal, and fronto–cerebellar, but also the fronto–limbic. As a whole, this disconnectivity is the result of a delay in both functional and anatomical cerebral maturation as part of an abnormal neurodevelopmental process that impracts attention, emotion, and somatosensory functions. From a neurobiological standpoint, the most agreed upon impairments seen in ADHD involve both the dopaminergic and noradrenergic systems. For example, we find a variation in the dopamine D4 receptor—correlated to prefrontal grey matter volume—and an increase in dopamine reuptake pump DAT1 binding, both of which are in favor of reduced dopaminergic transmission [3,11].

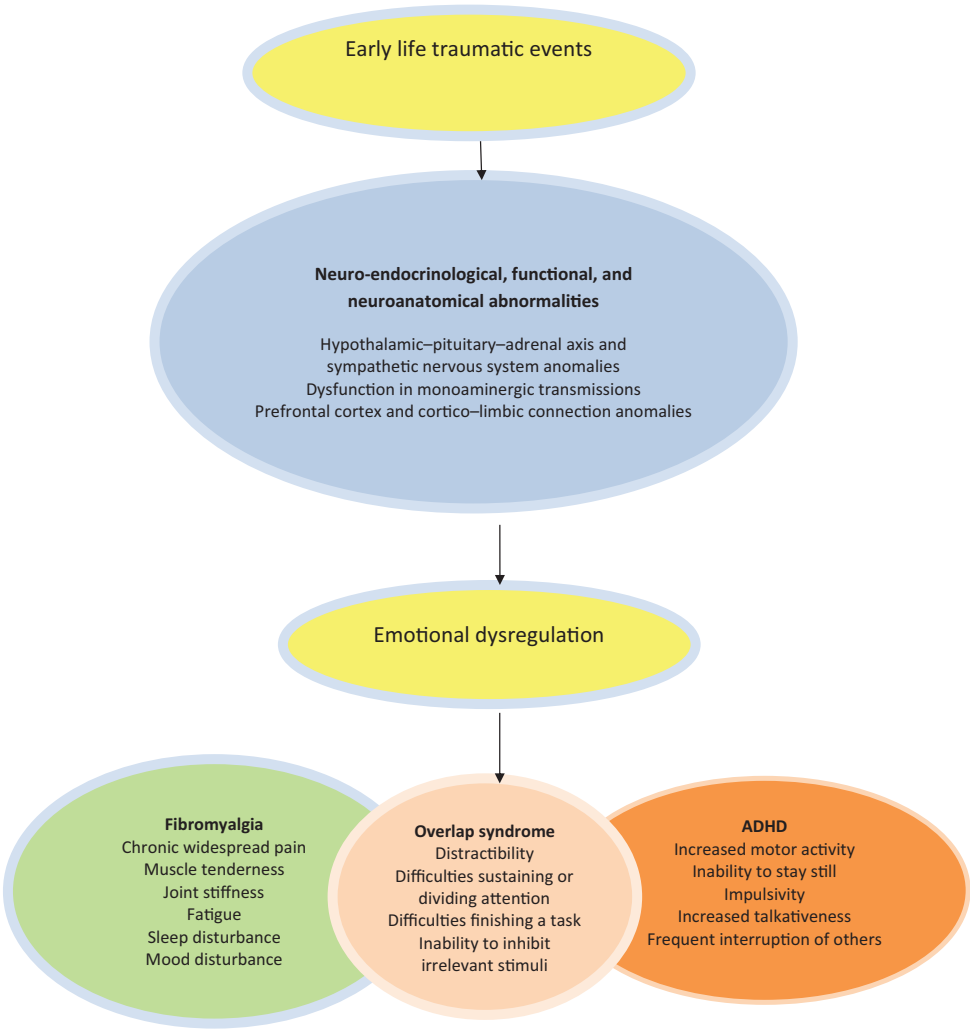

Figure 1 Shared early life events, pathophysiological processes, and clinical manifestations between fibromyalgia and attention deficit hyperactivity disorder.

Early Life Traumatic Events in FM and ADHD

Fibromyalgia

Early life painful physical incidents can cause long-lasting modifications in pain processing and perception in adulthood and do so by triggering the aforementioned central pain sensitization process [1,16]. More interestingly, however, is the fact that childhood psychological adversities may just as much induce alterations in future nociceptive transmission—greater temporal summation, increased number of pain locations, lower pain tolerance, and greater burden of pain [16].

Attention Deficit Hyperactivity Disorder

Single isolated traumatic life events can trigger subsequent conditioned somatic and behavioral responses upon later exposure to cues related to the initial incident. Chronic or repeated exposure to abuse or neglect, on the other, hand can produce much more profound impacts on neurodevelopment [17]. These trauma-induced alterations implicate such brain areas as the dorsolateral prefrontal cortex, the orbitofrontal cortex, and the anterior cingulate cortex, the same key areas studied as the anatomical substrates for ADHD symptoms, but also the hippocampus, the amygdala, the corpus callosum, and the hypothalamic–pituitary–adrenal axis [17]. In a clinical study on 364 victims of chronic abuse during childhood in the United States, 22% later developed ADHD [18].

Emotional Dysregulation in ADHD and FM

Fibromyalgia

Emotional dysregulation is a central element in patients with FM, explaining the better part of their psychosomatic, mood, and anxiety symptoms, but also a part of the cognitive difficulties encountered. As a matter of

fact, Duschek et al. [19], using an emotional variant of the Stroop test, provided evidence in favor of attentional bias and attentional delay in individuals with FM, driven by the emotional valence of the stimuli. In the experiment, patients took more time to identify the color in which words with a negative connotation were written as compared with neutral words, as more importance was given to the negative emotional value than to the neutral contextual cue (i.e., the color). This serves to show that inattentiveness in FM may be explained by a skewed focus on negative events and information, often to the abstraction of neutral or positive ones. Furthermore, pain severity had a much stronger correlation with this attentional interference than did depression, anxiety, or medications [19].

Attention Deficit Hyperactivity Disorder

Individuals with ADHD frequently present with difficulties in emotional recognition, regulation, and expression, although these symptoms are often overlooked. These dysregulations are mostly due to difficulties orienting attention toward and recognizing emotional cues, underlain by impairments in the striato–amygdalo–medio–prefrontal loop [20].

Conclusion

In conclusion, cognitive complaints in FM are often overlooked, under-rated, or dismissed as subjective epiphenomena of the frequently comorbid depressive or anxious disorders. However, as shown, these comorbidities explain only part of the complaints, whereas the bigger part remains standalone symptoms that may actually be the leftover inattentive symptoms of a childhood ADHD that went undiagnosed and untreated. In our current paper, we have shown that ADHD has a higher prevalence among FM patients, owing first and foremost to common neurobiological mechanisms. Second, this comorbidity is explained by the fact that ADHD may by itself trigger the development of central sensitization and FM because of the higher occurrence of physical accidents during childhood due to increased activity and impulsivity. The common pathogenic pathway for both ADHD and FM might be the emotional dysregulation that follows early life stressful events. Lastly, comorbid ADHD can therefore explain the cognitive symptoms encountered in FM patients (Figure 1).

The subset of individuals presenting with both FM and adult ADHD constitutes an interesting subpopulation that may display homogeneous pathophysiological processes, clinical presentations, and common therapeutic targets and treatment responses. Further studies should better delineate the characteristics of these patients to improve management and subsequently quality of life.

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