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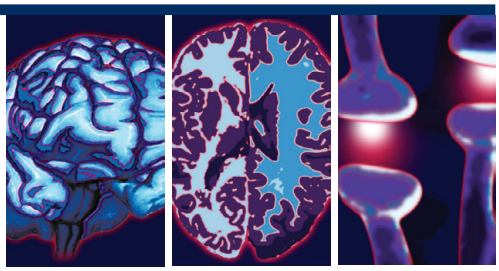

Central Sensitization: A Pathogenic Mechanism in Complex Undefined Diseases

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ABSTRACT

There is a common perception that complex undefined diseases manifested with diverse combination of symptoms and a difficult clinical diagnosis have a possible common physiological mechanism of disease production.

Physical or cognitive fatigue, widespread pain without arthritis, sleep, mood and autonomic disturbances as well as multiple intolerance involving drug, food, chemical agents, electromagnetic fields or other environmental factors may be included in this category.

Along last three decades, the existence of central sensitivity as a well established common pathogenic mechanism involved in abnormal symptom development emerged in diverse areas as pain, fatigue, food and environmental intolerance, as well as in the global chronic disease epidemic. The common fact of all of these disorders is a deregulation of the central control mechanisms at the limbic brain system. This may relate to amplification of pain and fatigue perception and disturbance of environmental tolerance and control of circadian rhythms and mood. This deregulation causes amplification of central somatosensory perception, but also a decrease of nociceptive inhibitory outputs. The final result is a chronic condition with central hyperexcitability and systemic disabling symptoms highly difficult to manage.

This article comments on the current significance to evaluate central sensitization symptoms and to consider these mechanisms in the development of complex diseases, as well as in the global chronic disease epidemic. We propose to include central sensitization to structuring a multidisciplinary concept addressed to improve scientific comprehension and clinical management of diseases, as well as future research directions on this field.

Keywords

Central sensitization, Fibromyalgia, Chronic fatigue syndrome, Multiple chemical sensitivities, Environmental Intolerance, Neuroinflammation, Limbic disorders, Complex diseases, Chronic disease Epidemic.

List of Abbreviations: CFS: Chronic Fatigue Syndrome, CS: Central Sensitization, CSS: Central Sensitivity Syndrome, EMF: Electromagnetic fields, FM: Fibromyalgia, MCS: Multiple Chemical Sensitivities, SSs: Symptom Severity scale, WPI: Widespread Pain Index.

Introduction

During the last three decades, most clinicians attending patients with complex undefined diseases have perception of a possible common involvement between different medical separated entities that share diverse combination of symptoms [1]. Those included physical or cognitive fatigue, widespread pain without arthritis, sleep, mood and autonomic disturbances

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as well as multiple intolerances involving drug, food, chemical agents, electromagnetic fields or other environmental factors [2-4].

The common fact of all of them is a deregulation of the central control mechanisms related to pain and fatigue perception, environmental tolerance and control of circadian rhythms [5,6]. This deregulation causes amplification of central somatosensory perception and development of chronic disabling symptoms [7].

Although this context is clear at clinical level and symptom presentation is quite similar in most patients, the absence of biological or morphological specific markers has supposed a difficulty to categorize these entities [4]. At the beginning, a persistent claim against to recognize these specific entities appeared, just suggesting to be in front of a somatoform-like paradigm without objective basis of disease [8,9]. However, based on epidemiological and clinical evidence, and the existence of a common physiological underlying mechanism of disease, a progressive scientific recognition has been established by diverse Committees and Medical Associations and case-diagnostic criteria appeared in some of these entities [2,10,11].

Thus, Chronic Fatigue Syndrome (CFS) was clinically defined in 1988 by Holmes et al. [12] after a task-force from NIH, USA. Pathological persistent physical and cognitive fatigue that does not improve at rest and exercise intolerance with post-exertion malaise is hallmark of this disease. Along the same period, the American College of Rheumatology defined the first clinical criteria for Fibromyalgia (FM) based on pain perception at pre-defined trigger points [13]. These criteria were modified on 2010 with a most waste and systemic inclusion of symptoms, also defining the intensity of involvement with the Widespread Pain Index (WPI) and the Symptom Severity scale (SSs) [14].

Those entities were recognized as specific diseases by the World Health Organization in 1990. In both cases, the initial criteria evolved to other more extensive, recognizing that fibromyalgia is not only a disturbance of pain perception or chronic fatigue is not just an exercise intolerance, being both entities characterized with a clear systemic and diffuse involvement with multiplicity of concomitant symptoms [15,16].

One of the most relevant facts that appeared along the natural course of disease is the high level of co-morbidity between them, achieving up to 80% of cases in fibromyalgia and chronic fatigue syndrome, thus suggesting a common physiopathological mechanism [17]. In addition to FM and CFS, other entities appeared as a co-morbid phenomenon in the natural FM-CFS course of disease [18]. Thus, the incidence of migraine, irritable bowel syndrome, temporo-mandibular disorders, restless leg syndrome, chronic pelvic pain, interstitial cystitis, sicca syndrome, chemical or environmental intolerances and others was described as highly related to either FM or CFS [9,19,20].

Another objective factor in patients with FM or CFS was the frequent appearance of symptoms related to intolerance to drugs, mainly active psychotropic, analgesic and anti-inflammatory drugs [21]. But this intolerance was amplified to food compounds or other multiple environmental factors [22]. Thus, these patients tend to avoid consumption of alcohol, caffeine, lactose, fructose, gluten or fat-rich nutrients because of a clear intolerance [23]. They were sensitive to environmental temperature or humidity changes [24], as well as to intense light or high-level of noise [25]. This reactivity was also amplified to the loss of tolerance to environmental irritant chemicals such as cosmetics, fragrances, chloride or phosphate biocides, solvents or hydrocarbon compounds that should be avoided [26,27].

The sensitivity to electromagnetic-fields (EMF) is the last element added to this series [28]. In this case, the subject develops symptoms when exposed to low intensity EMF of different origin in the spectrum of non-ionizing waves (wi-fi, mobile phones, computer screens, antennas). Those symptoms clearly improve when the subject avoids those EMF exposures [29].

The emergence of central sensitivity in the past 30 years linked to various complex undefined diseases may be associated with the global chronic disease epidemic [30].

The multiplicity of inciting agents that can get worse the course of this diseases leads to consider the concept of Exosome. This includes all these different physical, chemical or biological factors that may contribute from outside the human body in a cumulative and synergistic manner [31,32]. This concept also relates to the Endosome, considering changes induced in intestinal or visceral microbiota and also mood and stress-related changes [33]. Exposome would be the sum of exo and endosome factors, considering all their global and summation effect. The exposome may target a sensitive subject in a

subclinical appearance for time (masking), until this subject lost his biological tolerance capacity and symptoms appear (clinical phase) [34]. Claudia Miller et al. [35] generated the concept of toxic-induce lost of tolerance to define when central sensitization mechanisms appeared in front of persistent environmental low- level toxic exposure. Intolerance to food, drugs, chemicals, heat and environment factors may inactivate the anti-aging gene that is linked to mitocondrial apoptosis in the brain and other tissues [36].

Central Sensitization

The common mechanism that explains the multiplicity of symptoms in front of diverse exposure in susceptible subjects is central sensitization [5,6,37]. This is a neurologic inflammatory-based mechanism located in the limbic system that includes mid-brain associated structures such as the hypothalamus, hypophysis, amygdala, thalamus and cortical projections [38,39]. When a peripheral stimulus is generated in a susceptible individual, the conduction sensory system amplifies it at the dorsal roots (spinal hyperexcitability). This amplified stimuli still increases in power when received in the thalamus and projected to the limbic system and cortex. The result is an expanded input in the somatosensory brain with high-level nociceptive perception [7]. A central amplification occurs enhancing the pain response to noxious stimuli in amplitude, duration and spatial extent, establishing stronger brain memory [40]. Thus, sensory- afferent signals overwhelm the body's ability to filter them. The result is the generation of diverse abnormal symptoms such as pain, fatigue, insomnia, irritability or confusion. In addition to this increased input, the system does not produce adequate negative outputs to decrease or inhibit the stimulus. Since there is no decreasing of anti-nociceptive pathways, the response tends to be persistent and produces symptom maintenance [41].

This global mechanism generates an abnormal and progressively increased response over time, similar to the epilepsy wind-up or kindling phenomenon with a final additive effect [42,43]. This limbic abnormal amplification response was first described in neuropathic pain pathways [44,45], but later also corroborated for physical and cognitive fatigue [46] and chemical [47,48] or EMF sensitivity [28]. So, different external stimuli in nature (physical, chemical, biological or phychological), may generate a common phenomenon of abnormal limbic deregulation and a variety of amplified symptoms, that set up the Central Sensitivity spectrum of response (**Table 1**) [1,10,48]. In this process, anti-aging genes inactivation by environment factors may have a relevant role [30,49,50].

Evidently, development of CS mechanisms in a subject is compatible with the coexistence of other pathogenic mechanisms such as infection, autoimmune, auto- inflammatory, endocrine or autonomic deregulation disorders [4,7,9,18,51]. In fact, the sum of all of them may be additive and synergistic [5,6]. CS frequently appears after the onset of a specific medical entity, for instance in multiple sclerosis [52] or rheumatoid arthritis [53].

Symptoms that may appear in CS are diverse in nature and intensity, reflecting a systemic deregulatory failure [1,54]. **Table 1** describes the most frequent symptoms of CSS. Usually, at one time, the subject with CSS may share 5 to 8 different symptoms, being the clinical scenario diverse, pathomorphic and difficult to evaluate [1,2]. One of the peculiar characteristics in CS is the worsening of symptoms when the

Table 1: Main reported symptoms in the central sensitization clinical spectrum.

Pain (either diffuse of focal, persistent, oscillating) • Musculoskeletal • Cephalalgia • Abdominal • Pelvic-Gynecological
Fatigue • Physical (exercises intolerance) • Cognitive (short-term memory, attention, concentration) • Post exertional malaise
- Skin Itching- Burning
- Confusion
- Tremor - Myoclonia
- Blurry Vision
- Dry Eye - Dry Mouth - Skin Dryness
- Odynophagia
- Cough
- Dysphonia and Fonastenia
- Food Intolerance
- Nauseas
- Diarrhea
- Postural Hypotension-Tachycardia
- Dysthermia-Sweating
- Paresthesias
- Muscle Stiffness - Cramps
- Insomnia – Diurnal Somnolence
- Sleep Apneas
- Anxiety- Irritability- Stress intolerance
- Dysthymia - Depression

sensitization mechanism is over. For instance, subjects with MCS clearly develop symptoms when exposed to low-dose of chemical inciting products [48] or subjects with EMF sensitivity worsen when are exposed near to EMF at lo-intensity range [28]. Abnormal physical or neurocognitive fatigue increase when subject surpasses his exercise tolerance, a situation that usually coincides with the anaerobic exercise threshold [55]. Pain in Fibromialgia develops inadequately at low-level of activity and local pressure of sensitive areas, but is abnormally prolonged at rest [3].

Therefore, the CS spectrum of disease is large, and includes more than 50 different diseases where CS mechanisms may play a partial or significant role [1,19]. **Table 2** reflects the most usual clinical entities proposed to be almost partially affected by CS mechanisms [6,35].

Criteria for Central Sensitivity have been defined when coexist more than one specific disease and different areas of hypersensitivity affected in this large spectrum [10,54].

■ The relevance to consider central sensitization mechanisms

When evaluating patients with a diversity of non-explained symptoms or when they have already configured one or more CS specific diseases, the possibility that some of those symptoms to be mediated by CS mechanisms is relevant [5,6,19]. This is due to the implication of a peculiar scenario of disease development with multiplicity of clinical manifestations and a different therapeutic response [54]. Therefore, in the management of patients with CS, multidisciplinary approach and personalized care medicine is necessary [17,56-60].

For instance, we should not expect to find specific biochemical or structural changes explaining this disease [4,61,62]. There is no correlation between the intensity of biochemical inflammatory response and the clinical symptoms [5,63]. In addition, we should differentiate this CS neurological mechanism to other of somatophorm origin [9,11]. Because of this difficulty to approach patients' symptoms, in the initial symptom evaluation of CS disorders it has been proposed to use the short-form central sensitization inventory [64,65] and manage these patients in medical specialized areas [37,44]. Similarly, the response to treatment is only symptomatic and at low-intensity level [4,10,56]. Thus, just multi-factorial multidisciplinary approaches are able to get some symptom improvement in CS diseases. In general, pharmacologic symptom treatment should be individualized and complemented by avoidance of inciting agents, personalized physical exercise, dietary and environmental changes, psycho-educative adaptation support and cognitive behavioral therapy [66-68].

The oscillating course of CS also contributes to difficult interpretation of symptoms. Patient expectations usually differ from that possible to accomplish in CS disease management. This may cause dissatisfaction either for the patient, but also for the doctor and the health system [35,68,69].

Table 2: Most usual clinical entities proposed to be involved in central sensitization mechanisms.

• Fibromyalgia	• Seasonal affective disorder
• Chronic fatigue syndrome	• Traumatic stress disorder
• Multiple chemical sensitivity	• Post-depression syndrome
• Electrohypersensitivity	• Primary dysmenorrhea and Endometriosis
• Myofascial pain syndrome	• Restless leg syndrome
• Migraine headache	• Periodic limb movement disorder
• Tension-type headache	• Non–celiac gluten intolerance
• Burning mouth syndrome	• Irritable bowel syndrome
• Atypical odontalgia	• Intersticial-Irritative Cystitis
• Temporomandibular disorder	• Histaminosis
• Eye-mouth dry syndrome	• Attention deficit hyperactivity
• Visceral Pain Sensitivity Sd	• Vulvodynia/vulvar/vestibulitis Sd
• Complex regional Pain Sd	• Autism
• Tinnitus	• Postural tachycardia Sd (POTS)
• Sleep-Apnea	• Reflex sympathic algodistrophy (Sudeck)
• Raynaud (idiopatic)	• Idiopathic dysthermia

Conclusion

Current scientific knowledge concerning mechanisms of disease in central sensitivity is clear and consistent, opening an opportunity to better understand these complex diseases involved in this clinical scenario [2,4,37,41,45]. Consequently, we suggest a better doctor consideration in relation to ascertain this mechanistic explanation and specific rules of CS disease development. This may allow to structuring a more precise pathogenic multidisciplinary CS concept [70]. This will apply to improve the practical management on these complex diseases and offers a therapeutic target as well as future research opportunities [5,45]. On this sense, possibilities to modify the anti- aging genes [71] and introduce neuromodulation strategies [72] may be of interest in CS management. This paradigm should be necessarily projected and reflected on

a better explanation of disease to the patient and may contribute to improve the patient-doctor relationship on this field, as well as a better CS patient follow-up in specialized areas.

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