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CHRONIC FATIGUE SYNDROME: A REVIEW

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ABSTRACT

Myalgic encephalomyelitis also known as chronic fatigue syndrome (ME/CFS) is a group of diseases that affects millions of individuals throughout the world and is basically characterized by debilitating tiredness that lasts for 6 months. The precise mechanism of the pathophysiology of ME/CFS has yet to be discovered however various studies indicate that cytokines, immunoglobulins, T and B cells, Natural killer cells (NK cells), viral infection, and diminished hypothalamic-pituitary-adrenal axis response are involved in it. Currently, no particular pharmacological treatment is available in the market for the management of ME/CFS. If available they provide only symptomatic relief. Thus, the purpose of this review is to explicate different pathophysiological approaches to understanding the paramount concepts of ME/CFS and open the vista for pharmacological treatments that aid in better treatment beneficial in ME/CFS.

KEYWORDS: Cytokines, Natural killer cells, T and B cells, ME/CFS.

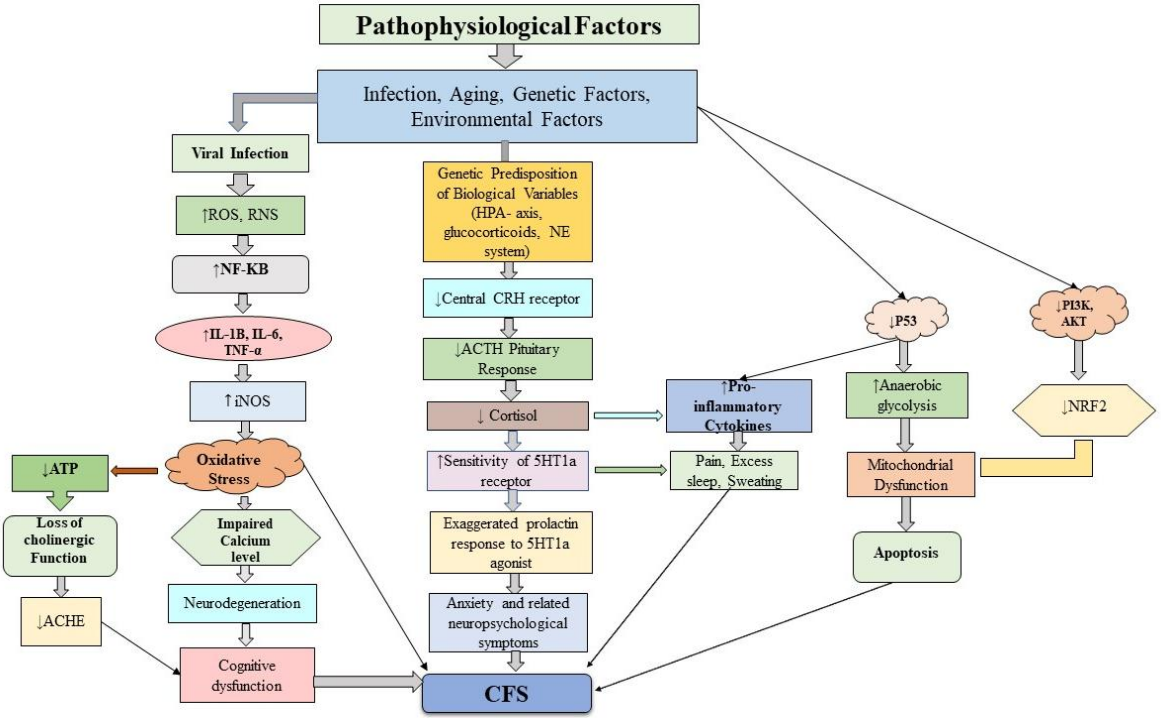

Fig. 1: Factors involved in pathophysiology of CFS.

1. INTRODUCTION

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) is a complicated condition that is characterized by persistent fatigue exacerbated by physical activity, Rest has no effect on CFS.[1] Evidence indicated that CFS affects adults, aged between 20 to 45 years with a female to male ratio of 3:1.[2] However, determining the true frequency of ME/CFS is quite tough, as there is no tool to diagnose the individuals with fatigue and other clinical signs.[3] CFS is characterized by debilitating tiredness lasting for at least 6 months, fever, pharyngitis, sore lymph nodes, headache, myalgias, sleep problems, neurocognitive issues, and depression Fig. 2.[4]

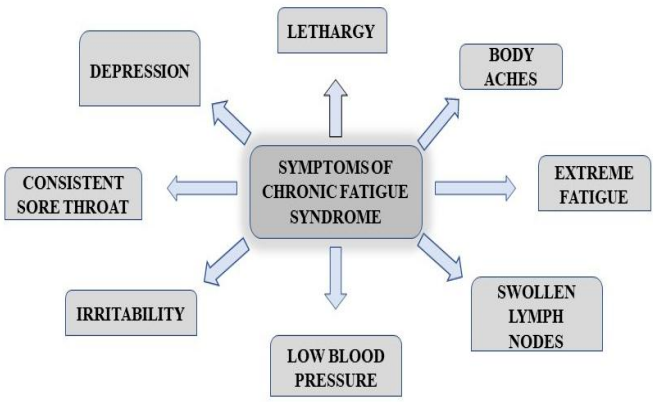

Fig. 2: Symptoms of CFS.

The majority of patients with CFS reported chronic broad persistent pain, such as arthralgias and myalgias, in addition to crippling fatigue.[5] The pathological threshold of fatigability in ME/CFS is frequently achieved with minimal physical or mental exertion, with decreased ability to perform the same activity within the same or multiple days.[6] The pathophysiology behind CFS is not clear, but there is compelling evidence that at least some ME/CFS patients have an autoimmune origin. Research have shown a magnificent role of cytokine, immunoglobulin, T- and B-cell, and natural killer cell in ME/CFS.[7] Miscellaneous factors such as mental problems, infectious agents, metabolic abnormalities, contagious, and hereditary elements in CFS, the Immune system, and population-based documentation all collectively indicated that ME/CFS is an infectious illness and the host characteristics influence susceptibility to the illness since the virus lingers in patients and can be transferred through casual contact.[8] Fig.3. A large number of researchers have also been battled to understand its pathogenesis, which includes viral infection, neuroendocrine irregularity produced by diminished hypothalamic–pituitary–adrenal (HPA) axis activity, immunological impairment induced by aberrant cytokine production, and neuroinflammation.[9] Mild hypocortisolism and decreased hypothalamic–pituitary–adrenal axis response has been found in neuroendocrine research.[10] Epstein-Barr virus (EBV), human herpesvirus (HHV)-6, and human parvovirus B19 are among the infectious etiologies suspected of causing CFS. It has been found that Anti-HHV-6 IgM antibodies and HHV-6 antigens were found in the peripheral blood of patients with CFS than in the general population, indicating a higher prevalence and reactivation of the virus.[11] Free radicals are also important in the pathophysiology of CFS. Elevated levels of nitric oxide (NO) and peroxynitrite (NO_2^2), are found in ME/CFS, with disturbance in neural signaling and mitochondrial function. Moreover, there is abnormality in energy metabolism in ME/CFS.[12],[13] Lifestyle constraints, increased job absences, social isolation, and depression are all possible effects of CFS. The literature review indicated that in CFS there is an increase in the level of pro-inflammatory cytokines, nuclear factor- κB (NF-κB) with inactivation of p53 that disrupts aerobic mitochondrial activities, leading to a greater reliance on glycolysis under anaerobic conditions, increased lactate levels, decreased skeletal muscles mitochondrial density, and lower endurance with physical exercise. Increased ROS decreased the p53 levels and thereby increases NF-κB, which in turn causes a marked release of pro-inflammatory cytokines such as IL-1, IL-6, TNF alpha, and cyclooxygenase (COX-2).[14] NF-κB, p53, and glycolysis all have a connection. In contrast with CFS, Through IKKa and IKKb kinase activity too elicited its role in CFS that is linked to NF-κB activation.[15] ME/CFS influences people of different

ages, ethnicities, and socioeconomic backgrounds. In sporadic ME/CFS, the highest ages of onset are 11–19 years in young patients and 30–39 years in adults.[16] According to several epidemiological research, the worldwide prevalence of CFS ranges from 0.2 percent to 2.7 percent. The white population appears to have a higher prevalence than the non-white population.[17] A 1.5 percent prevalence incidence of CFS-like illness was discovered in various regions of the world.[18] ME/CFS left 27% of patients bedridden and 29% housebound, leaving 50% unable to work full time and 21% unable to work at all.[19] Along with CFS, 90% of people suffer from anxiety (48%), depression (43%), fibromyalgia (39%), irritable bowel syndrome (IBS) (38%), and migraine headaches (37%).[20] One of the causes is a lack of awareness of ME/CFS, basically due to the complex history of the disorder.[19-21] Evidences indicated that the prevalence is much greater in the age group of 40 to 70 years old specially in the women.[17] However, CFS is rare in childhood and adolescence: only 0.06% to 0.32% of children from 5 to 15 years of age fulfill the US Centres for Disease Control and Prevention (CDC) criteria for CFS.[22]

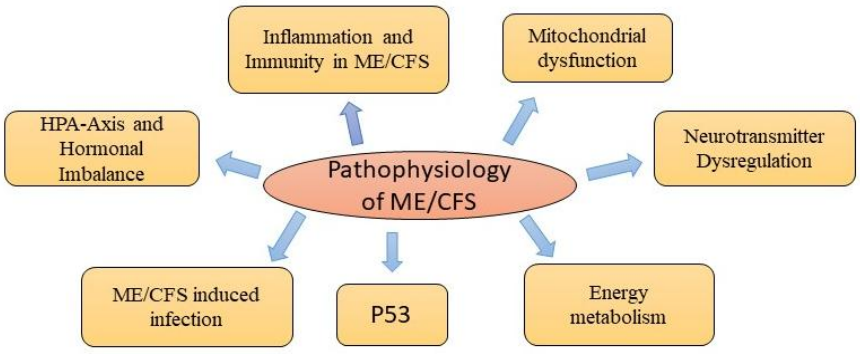

Fig.3: Indicated mediators involved in ME/CFS.

2. Pathophysiology of ME/CFS

2.1 Inflammation and immunity in ME/CFS

In ME/CFS the homeostasis of the immune system is dysregulated. This implies ME/CFS patients will frequently have symptoms associated with immunological abnormalities, such as increased susceptibility to infections, persistently enlarged and sensitive lymph nodes, and a high temperature.[23] ME/CFS affects the immune-type cells of the CNS, such as microglia and astrocytes. In ME/CFS, there are increased levels of microglia and astrocyte activity, indicating the role in inflammatory processes. Microglia and astrocytes have been suggested to have a role in the onset and maintenance of immunologically caused ME/CFS, possibly via

enhancing Blood-Brain Barrier (BBB) permeability.[24] In ME/CFS there is a great impact of acute-phase reactants with decreased antioxidants such as zinc and coenzyme Q10. As explained earlier, all of them had a great impact on the dysfunction of mitochondria, and aberrations in intracellular signal transduction and activation of apoptosis pathways.[25] Oxidative stress has been found to be higher in CFS patients in several investigations.[26] Studies have shown that oxidative stress indicators (such as isoprostane, oxidized LDL, and iso-prostaglandin F2) are elevated in the blood, as well as a reduction in antioxidant capacity as measured by glutathione levels (GSH), Superoxide Dismutase Level (SOD).[27] A viral infection might activate antiviral pathways fast, IFN-γ too plays a vital role in response to viral infection in CFS.[28] IL-1, IL-1, IL-4, IL-5, IL-6, IL-12, and IL-2 are cytokine levels that are frequently reported as raised, whereas IL-8, IL-13, IL-15, and IL-23 are reduced.[29] Furthermore, TNF-α and IFN-γ levels are increased as well as those of NF-κB, a transcription factor regulated by cytokines such as TNF-α and IL-1β.[30]

2.2 Role of Hypothalamo-Pituitary-Adrenal (HPA)- axis and Hormonal Imbalance

The HPA axis is an essential aspect of the neurobiological stress system, which consists of a variety of networks that create complicated pathways and contribute to the maintenance of homeostasis. It is impacted by numerous variables such as physical and psychological stresses.[31] Patients with ME/CFS may have a disruption in the amounts of hormones generated by the HPA axis. The most reproducible biological result in ME/CFS adult patients is downregulation of the HPA axis, represented by a modest cortisol-awakening response in the salivary glands.[32] Inactivity, sleep disturbances, mental comorbidities, medication, and chronic stress have a great impact on the activity of HPA.[33] In ME/CFS there is a marked increase in corticotropin release hormone (CRH), followed by a decrease in CRH receptors (CRHR) on pituitary corticotropes neurons.[34] Adrenocorticotrophin Hormone (ACTH) too elicited its role in the pathophysiology of CFS as ACTH regulates plasma cortisol, which has a linear connection in ME/CFS patients.[35] Several investigations have discovered that in ME/CFS patients, the morning peak of ACTH is negligible. In the majority of fibromyalgia patients, dysfunctioning of the HPA-axis is also present. Various explanations have been proposed, including hypothalamic CRH secretion suppression, pituitary CRH receptor insufficiency, and adrenal atrophy owing to prolonged under-stimulation by low ACTH levels.[36] Hypercortisolism may be due to impairment in central nervous system signaling, such as limited output of adrenocorticotrophic hormone (ACTH); decrease in the size of the

adrenal gland, and increased negative feedback of the HPA axis and decreased ACTH response.[37]

2.3 Neurotransmitter dysregulation

Microglia and astrocytes can be activated in a sequence by chronic neuroinflammation. IL-6, IL-1, ROS, RNS, COX-2, prostaglandin E2 (PGE2), glutamate, and, in some cases, quinolinic acid are just a few of the neurotoxic molecules that are secreted by activated microglia. The creation of these neurotoxins has a considerable and unfavourable influence on the release of neurotransmitters.[38] Neuro-glial activation signalling is connected to the increased production of neuro-excitatory neurotransmitters and immune-inflammatory mediators.[39] The serotoninergic system is the most prevalent neurotransmitter abnormality linked to ME/CFS.[40] In addition, the β2-adrenergic receptor and the catechol-O-methyl transferase (COMT) were found abundantly in ME/CFS patients.[41] The activity of the COMT enzyme has been shown to be negatively related to catecholamine levels.[42] Increased ROS and RNS in the CNS can potentially impede dopaminergic neurotransmission by preventing dopamine receptors from being activated.[43] Proinflammatory Cytokines (PIC) can have serious pathogenic implications in the brain, either directly or indirectly.[38] Glutamate neurotoxicity can be caused by activated microglia releasing PICs and glutamate, as well as impaired glutamate absorption by active astrocytes, Causing severe destruction to glutamatergic neurons and their neurotransmission.[44] The synthesis, reuptake, and release of serotonin can all be affected by increased CNS PIC levels and consequent upregulation of the p38 mitogen-activated protein kinase (MAPK) signaling pathway.[45]

2.4 Energy Metabolism and Mitochondrial Dysfunction

Metabolic needs vary depending on the resting, activated, or differentiated stage. During an active state, the metabolism shifts to aerobic glycolysis in order to supply adequate energy and bio-precursors to enable rapid cell growth and immunological activities.[46] As the anaerobic threshold was achieved during the exercise testing with increasing workload, it's possible that mitochondrial ATP production was reduced. The mitochondria could no longer make enough ATP to keep up with the workout, thus anaerobic glycolysis in muscle had to step in and provide the extra ATP, as seen by lactate formation.[47] Mitochondria are also engaged in redox signaling and cell danger responses, among other critical biological functions. Clinical symptoms in ME/CFS may be caused by dysfunction in any of these functions.[48] Therefore, the levels of particular mitochondrial proteins, the synthesis of ATP,

and, more recently, oxygen consumption of live plated cells have all been utilized to evaluate mitochondrial dysfunction in ME/CFS. The first signs of mitochondrial dysfunction in ME/CFS were structural abnormalities in the mitochondria of skeletal muscle cells.[49]

2.5 ME/CFS induced Infection

Candida albicans, Borrelia burgdorferi, Enterovirus, Cytomegalovirus, Espumavirus, Retrovirus, Borna virus, Coxsackie B virus, and hepatitis C virus (HCV) have been associated with CFS. Various other viruses, such as the Epstein-Barr virus (EBV), the human herpes virus (HHV)-6, and the human parvovirus B19, as well as intracellular bacteria, can also cause this condition.[50] Viral infections, which cause activation of ROS/RNS and various inflammatory mediators, can activate NF-kB, a critical transcription factor that could function as a provoking factor in patients, propelling an inflammatory rush. When activated, NF-kB travels from the cytoplasm to the nucleus, where it binds to the DNA promoter sequences of inflammatory mediators such as IL-1, IL-6, and TNF-, as well as O&NS mediators such as cyclooxygenase-2 (COX-2) and inducible NO synthase (iNOS).[51],[52] Many CD^{4+} and CD^{8+} cells too play a vital role in ME/CFS.[53] Human herpesviruses have been reported to alter the integrity and function of NK cells, T and B cells function, and cytokine production that resulting in ME/CFS typical symptoms. Furthermore, it too had a severe effect on neurons and immune cells that leads to brain damage.[54] In addition to this Parvovirus B19 also cause ME/CFS as it activates NK cells which causes neuroinflammation[55] Similarly, Enterovirus leads to muscle dysfunction by activating NK cells.[56]

3. Management of ME/CFS

Despite the Pathophysiology of ME/CFS is not so clear but management acts as a barrier in ME/CFS. Hence, the management of ME/CFS cures 88% of patients with analgesics, 52% with hormones, 41% of patients with antidepressants along with allergy-related pharmaceuticals (32 percent), gastrointestinal therapy (30 percent).[57-58]

3.1 Pharmacological Therapy

Antidepressant medications such as Amitriptyline, Desipramine, Citalopram, Fluoxetine, Paroxetine are given to patients with ME/CFS. Management with corticosteroids too have positive results in patients with ME/CFS. Immunotherapy drugs eg. Ampligen, Immunoglobulins, Alpha interferons, TNF-α inhibitors, and nutritional therapy with Carnitine, CoQ10, Vitamin B12, Vitamine C, Folic Acid, Zinc attenuated the symptoms of

ME/CFS. Moreover, anticonvulsants drugs such as Lamotrigine, Gabapentin, Topiramate, pregabalin and stimulants such as Atomoxetine, Sodium oxybate, Methylphenidate with muscle relaxants like Methocarbamol, Orphenadrine, Tizanidine, Cyclobenzaprine too showed ameliorating effects.[59],[60],[61]

Table 1: Indicated Line of treatment for CFS.

Medication	Example	Intervention	Adverse Reaction	References
NSAIDS	Ibuprofen and naproxen	Relieve frequent or severe joint and muscle pain, headaches, reduce fevers and inflammation.	Gastrointestinal distress and bleeding.	[57]
Tricyclic antidepressants	Amitriptyline, Doxepin, Nortriptyline, Desipramine	Symptom relieve, improve sleep, and relieve pain in much lower doses than those used to treat depression. Has anti-anxiety effect and improve locomotor activity.	Sedation, urinary retention, sexual dysfunction, weight-gain comorbidities.	[57]
Selective Serotonine Reuptake Inhibitor	Fluoxetine, Sertraline, Paroxetine	Helpful for anxiety/depression and other mood disorders in patients with ME/CFS, as well as patients with chronic neuropathic pain.	No specific adverse reactions have been described in the RCT.	[58]
Antiviral Drugs	Rintatolimod, Valganciclovir	Enhance the NK-function and influence the 2-5A-synthetase pathway, producing an objective improvement in exercise tolerance and a reduction in ME/CFS-related concomitant medication usage.	Is a well-tolerated medication in the right dosage.	[59]
Monoclonal Antibodies	Rituximab	Decrease the activity and number B-cell by inhibiting CD20, thus reducing inflammation. Studies demonstrate symptoms alleviation and improvement in quality of life within a 12-month follow-up.	Neutropenia, and increase of severe infections.	[60]
Complementary and alternative medicine.	Nutritional supplements, Acetyl-L-carnitine, Essential fatty acids, Magnesium.	Nutritional supplements may improve ME/CFS-related physical and mental fatigue in patients with specific nutritional deficiencies**.**	No specific adverse reactions have been described in the RCT of nutritional supplements.	[61]

3.2 Non- pharmacological Therapy

The problem with synthetic drugs lies in their maximal ADRs. so, there is a need for herbal drugs for the treatment of ME/CFS. Various evidence has indicated the role of herbal drugs such as Uncaria tomentosa, Panax ginseng, Eleutherococcus senticosus, Cordyceps sinesis, Withania somnifera, Glycyrrhiza glabra, Gynostemma pentaphyllum, Trichopodacea in the management of ME/CFS.[62] (table 2).

Table 2. Herbal Drugs used in the management of Chronic fatigue syndrome.

Herbal Drugs	Family	Action	References
Cat's claw (Uncaria tomentosa)	Rubiaceae	Immune system Stimulation	[60]
Ginseng (Panax ginseng)	Araliaceae	Anti-inflammatory	[60]
Trichopodacea	Trichopus zeylanicus	Anti-fatigue	[60]
Siberian ginseng (Eleutherococcus senticosus)	Araliaceae	Stimulant, Anti-Inflammatory	[63]
Liquorice (Glycyrrhiza glabra)	Fabaceae	Immunomodulatory	[63]
Rosenroot (Rhodiola rosea)	Crassulaceae	Anti-depressant	[63]
Ashwagandha (Withania somnifera)	Solanaceae	Immunomodulatory	[64]
Jiaogulan (Gynostemma pentaphyllum)	Cucurbitaceae	Anti-oxidant	[64]
Caterpillar Fungus (Cordyceps sinesis)	Clavicipitaceae	Stimulant	[64]

4. CONCLUSION

Due to a lack of knowledge of the etiology, the natural history of ME/CFS, and constraints in pathophysiology, the varied presentation of symptoms, and their severity have been difficult to describe. Various pharmacological and non-pharmacological therapies have been adopted for the management of chronic fatigue syndrome. The diagnosis and therapy of chronic fatigue syndrome should be multifaceted and adapted to the specific needs of each patient. Thus, there is a need to explore more targets that are involved in the progression of ME/CFS. This will open the vista and helps us to treat the symptoms of ME/CFS in order to ameliorate the quality of life.

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Conflict of Interest

The author holds no conflict of interest with anyone.

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