Review

Chronic Fatigue Syndrome, Viruses and Related Conditions in Women: The Liver Link

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Chronic Fatigue Syndrome, Viruses and Related Conditions in Women: The Liver Link

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Abstract: Chronic Fatigue Syndrome (CFS) can be triggered by different factors and create a complex health situation. In the last decades incidence has been increasing. This situation is a clear example of how humans, viruses, and the environment are all connected. In the 90s cases related to CFS, complaints about a feeling of chronic fatigue, inability for everyday tasks, dull pain, cephalalgia, depression, anxiety, poor concentration. Clinical tests for EBV, HHV, CMV, IgG, IgM, T4 and T8 subsets were tested, along with hormones and hemogram tests. Most of the cases were women. The timeline of the medical history showed also myomas, breast lumps, premenstrual syndrome previously to CFS development. The nature of these conditions promoted the idea of a possible common link among them and CFS. Some cases also suffered from allergies, food intolerances, candidiasis, intestinal impairment, thyroid implications, endometriosis. As an initial working hypothesis, The Liver Link (TLL) was proposed in order to understand those different conditions affecting body, mind and emotional wellbeing. Considering liver implication can make a difference in treatment and recovery. Low grade inflammatory conditions are related to Th2 predominance and liver functions. Functional disharmonies are very important because they usually still do not appear in any conventional tests. In 2002, TLL was presented as a framework to explain the concomitance of CFS and other conditions and the relationship with some viruses such as EBV, HHV, CMV, as a lecture in a congress at the University of Westminster (London). When SARS-CoV-2 outbroke, TLL helped to warn about the post-covid syndrome more likely to occur in specific individuals.

Keywords: chronic fatigue syndrome; epstein barr virus; liver; Th1—Th2; women's health

1. Introduction

The longer it takes for a case to be diagnosed, the more complex it will be, as it will have evolved over time. Evolving means not only more severe already existing conditions but apparently new ones. This is a situation found in Chronic Fatigue Syndrome patients. More conditions can come to the complex table, such as, different autoimmune diseases (rheumatoid arthritis, multiple sclerosis, thyroiditis), several hypersensitivities like chemical hypersensitivities, endometriosis, leaky gut and other intestinal damages, microbiotas disharmonies, SIBO, insulin resistance, chronic urinary infection, chronic neuralgias, chronic migraines, anxiety, depression and even oncologic conditions. It can be noticed this means a variety of conditions affecting physical, mental and emotional life. Any person, man or woman, suffering a similar situation shares a feeling of disappointment, social and medical misunderstanding, loneliness, anxiety, depression, lack of motivation in life and daily activities.

The implications of the liver functions in general health fall beyond the most apparent relationships in which a liver diagnosis exists. In 2000, while teaching a group of students about female physiology and physiopathology, the idea of a specific seminar which was called "Understanding the liver" came to be a reality. The content grew and in 2002 it was presented at the University of Westminster (London) named The Liver Link. This paper is a brief presentation of more than three decades of work trying to compose a 4D puzzle with several conditions appearing one after the other, then being suffered at the same time, which had some points in common in the

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physical level: liver, viruses, chronic fatigue. Although women are more represented, men are also included.

Implicit in "The Liver Link" is the need to study and to reconsider all the areas of the individuals lives and the environment. None of us live separated from the environment. Certain lifestyles, a heritage of contamination of air, water, food, the excessive presence of toxins in our body; viruses, bacteria, animal species travelling as fast as a commercial flight, arrive in different continents or new areas, as invasive species exposing humans, animals and plants to new threats and diseases.

The liver is related directly and indirectly to all our organs. Liver fulfils the essential functions of maintaining balance and functionality by purifying and detoxifying our bodies and brain, maintaining a proper level and flow of hormones and other substances and information in the organism, preventing blockages and mass formation, promoting clarity in the sensory organs and physical and mental agility, among other functions. Taking care of the live can take advantage of integrative treatment approaches which offer the possibility of a combination of chemical or conventional pharmaceuticals with complementary nutrition and herbal therapy.

There are situations in life that teach us as time goes by. Chronic Fatigue Syndrome happens to be one of these situations: A major and global physical and mental health challenge for Health Sciences, Nature Science even for Education and Technologies. The Liver Link as a framework can help us in this endeavour.

Each of us must be careful to ensure that our lifestyle, the air we breathe, the food we eat, the water we drink, are in accordance with overall health. Beyond this, we are responsible for the planet from our human scale. New generations are pushing hard.

2. Central Control System: the "Intel" Taking Care 24x7

Human beings live in constant contact with the environment: the air we breathe, the food we eat, the water we drink, an important variety of resources, climate, but also other inhabitants such as animals or microorganisms Environment also includes other human beings. Despite the effect of human beings on the environment, here we shall consider our basic need of protection, feeding, adaptation, learning how to keep us alive, deal with threats and changes, resilience and recovery from damages 24 hours each and every day. Quite similar in essence to our ancestors´ life.

Likewise, all the cells in our bodies live in constant contact with their environment, which is us as a whole. Our body is their environment. Our environment affects cells themselves too. Cells communicate with cells, so that tissues and organs are communicated among them. Extracellular matrix is the space in which important exchanges and homeostasis occur. Globally, body and mind are connected and can affect each other. Although mind is a concept we "understand"; "mind" itself is difficult to define depending on the area of knowledge, and usually is taken as synonymous with the brain. Here we will use mind as a general term including thoughts, learning, intelligence, emotions, feelings and all this subtle part of ourselves.

Immune, nervous and endocrine (hormonal) system is a functional unit, which we refer to as the Central Control System (CCS). CCS continuously controls any change coming from outside or happening in our body, even in our minds, and creates responses to maintain and /or regain a healthy balance. Necessarily, CSS is based on the "intel" and working 24x7.

Our immune system basically is vigilant, receiving information, paying attention to any change, in order to detect if anything around us, in contact with us inside us, is not ours and /or could be a potential pathogen. Damaged, infected and mutated cells, toxins, toxics, microorganisms are also recognised as a threat. When a potential pathogen is detected, the immune system acts correspondingly. Specific immune cells, several chemicals not only from the immune system, but also neurotransmitters and hormones are involved in order to support the defence actions. Once the threat has been overcome… recovery and reconstruction is mandatory.

Immune system is not only activated when physical threats are detected, but also when we face certain emotions, situations or thoughts that our brain perceives as threatening.

Anything, any situation, even a person, that is recognised as a possible risk to our life or mental and physical well-being is a source of stress and can activate a defensive immune response, along

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with nervous and hormonal actions. Thus, different manifestations (signs and symptoms) will result. Hans Selye (1907 – 1982) was a pioneer in studying the stress response. its relationship with physical illness and how to take advantage of stress. Hence, the sentence: "Stress is not harmful itself".

Selye's work was also related to repeated exposure to stress, how the body intends to maintain the homeostasis. He proposed adrenal hyperactivity or adrenal fatigue was involved in cases of long stress and the basis of dis-adaptation syndrome. He was nominated for the Nobel Prize in 1949 in recognition of his work.

Stress is usually defined as a fight or flight response in an acute stress situation. But in the face of a threat one can also become paralysed, unable to move out of fear, even with sphincter incontinence.

Although the same pathogen is expected to create similar responses and manifestations, practice shows that not every person develops exactly the same response against the same pathogen or stressful experience. Symptoms can vary in terms of variety, intensity, severity and duration.

Individual reactions may be different depending on each person' own experience: previous contacts with the "pathogen", previous conditions, pharmaceutical treatments, physical and mental strength, habits, lifestyle, resiliency and also depending on beliefs about a certain condition, problem or disease.

Often our body is repeatedly in contact with the same pathogen, such as a virus or bacteria. Fortunately, our immune system is a quite perfect example of machine learning. Our immune systems create T and B memory cells helping us in case of further contact. B memory cells produce antibodies which bind antigens found in the pathogens to promote its destruction. T memory cells destroy those cells that have been infected and they also can support B memory cells in producing antibodies.

Fortunately, nowadays mental health is out on the stage and looking for psychological support is not something to hide anymore. Dealing with everyday life is not always easy. Global health can be supported by taking care of our mental and emotional life. Some areas are especially important as hormonal and immune balance, regular neurotransmitters availability, nutritional situation, among others. This author highlights the importance of taking care of a person as a whole. Proper help allows the immune system and brain to learn how to overcome painful experiences, to understand all our emotions and to face future problems. Memories from past illnesses, injuries, traumatism can be linked to mental and physical experiences and they can rise up later in similar circumstances.

When a new menace appears, our CCS react the best it is able to. Inflammation is a first and foremost quick general response to pathogens presence. Inflammation process is an astonishing coordinated response including immune cells, cytokines, neurotransmitters, hormones, in order not only to prepare the area and whole body for a defence battle, but also to alert our mind and prevent us from doing movements or activities that could result in failure. Pain is one of the main symptoms that inform us about the place where the damage is happening, preventing us from doing actions that could increase the damage. Fatigue is also a key symptom that promotes resting and sleep. Rest and sleep save energy that is needed to confront the pathogen.

Liver, kidneys, intestines, blood and lymphatic vessels, skin, all the inner cellular lining of the mucous walls and their biotas, all of them, play very important roles in general defence and restoring balance, it is homeostasis.

3. Chronic inflammatory processes and microorganism implication

Classical classification of immune system functions into cellular and humoral, even into Th1 and Th2 (regarding T cells helper 1 and 2) has evolved increasingly over the last decades due to the number of discovered cytokines. However still Th1 and Th2 is a simple way to express which main type or defence (cellular, humoral, pro-inflammatory or anti-inflammatory) prevails in specific cases and diseases.

Th1 and Th2 patterns act at the same time via their cells and substances, although Th1 is considered as the cellular defence and Th2 as the humoral defence. Correlated to aggravations observed in practice, even in mild situations, Th1 and Th2 actions show different patterns. Th1 and

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Th2 intensity change along a 24 hour pattern, waving in a circadian rhythm: Th1 appears to be stronger during day time, while Th2 actions are weaker; on the contrary: Th1 "slows down" at night while Th2 increases its actions. These ups and downs follow a pattern not completely understood up-to-day. In the 90s while studying inflammation in CFS, these waves were related to cortisol peaks that may vary according to sunrise and dawn. However, more hormones, neurotransmitters are involved. It has been observed that jet lag crashes the regular cycle of Th1 and Th2 and certain inflammatory conditions and responses can increase such as allergies [1]. It has been proposed that the interlinked relationship between cortisol, oestrogen, thyroid, serotonin, immunomodulators and others, may be involved in inflammatory conditions and chronic viral conditions, thus involving liver functions. Factors that can trigger a Th1 / Th2 imbalance are mentioned below.

For our purposes, this paper is focused on proinflammatory and anti-inflammatory functions. The wide implications of redox stress producing substances, such as, free radicals, reactive oxygen, nitrogen or sulphur- species, nitric oxide, superoxide dismutases, glutathione peroxidase, catalases and the whole range of redox signalling processes are clear in the general biochemical chains of the area of this topic. However, explaining the chemical reactions involved in detail is beyond the scope of this review.

Th1 pattern is mainly related to antiviral and anti-bacterial defence, intracellular pathogens, oncologic cells recognition and destruction via Natural Killer (NK) cells. Cytokines such as Interleukins 2 and 12 (IL2, IL12) and interferon-γ (IFN-γ) are key to this Th1 pattern.

Th2 pattern is mainly related to defence via antibodies. inflammatory actions in the extracellular domain, and defence against allergens, toxins, parasites and bacteria. Key substances: Tumoral Necrosis Factor (TNF), interleukins 4, 6 and 10 (IL4, IL6, IL10)

Th1 and Th2 control each other to maintain a proper balance and a healthy state. This control is crucial: Th1 and Th2 can promote or inhibit each other in order to promote an inflammatory defence and at the same time to diminish and stop via anti-inflammatory actions so that inflammation does not become excessive and creates damage. Specific cytokines such as IL4 can regulate both Th1 and Th2 [2] [3].

The delicate balance between Th1 and Th2 is lost under certain circumstances. In practice, some imbalances can occur. Here we consider the specific case in which the Th2 pattern prevails over Th1.

This shift in which Th2 is over-expressed prevails in chronic viral conditions such as EBV, HHV, CMV, hepatitis C in which NK cells may be diminished.

Immune system fails to be competent against these viruses: Decreased or functional insufficiency of Th1 means a loss of the ability to keep under control infections acquired in the past, i.e. EBV, HHV, HPV or even fungi, thus they can be reactivated. Due to the Th2 / Th1 imbalance chronic inflammatory processes and complex post-viral syndromes may develop [4].

4. Etiology for the Th1 to Th2 predominance shift

Over the last decades several factors have been collected as promoters of the Th1 to Th2 prevalence shift by observing the clinical and biological stories of patients suffering chronic fatigue and/or post-viral syndromes. Collecting aetiology while examining a single individual is difficult. The development of these situations may take several years and involve several factors at the same time or one after the other. Often patients are not aware of the possible triggers of their own situation. Th2 predominance shift is not created by an isolated factor, but by a combination of actors.

These are some factors to consider. The following list intends to create some associations between these factors in terms of physiopathology.

- Toxics and toxins exposure and cumulative impact.
- Environmental pollutants.
- Irritant agents.
- Carbamate and organophosphate insecticides.
- Heavy metals such as mercury, lead, cadmium.
- Hormonal disruptors.

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- Microplastics.
- Liver functions insufficiency.
- Previously acquired virus infection, i.e: EBV, HHV, HPV, SARS-CoV-2
- Repetitive infections such as *Escherichia coli*.
- Vaccinations.
- Toxins inoculation as in Lyme disease (*Borrelia*), neurotoxins, vector insects.
- Leaky Gut Syndrome, several intestinal impairments.
- Hydrochloric acid and enzyme insufficiency.
- Extracellular matrix damage or incompetence.
- Hormonal imbalances.
- Adrenal insufficiency or adrenal fatigue.
- Glucocorticoids misuse. Opiate painkillers misuse.
- Chronic pain.
- Poor sleep.
- Poor nutrition.
- Physical stress.
- Psychological stress.
- Psychological and/or physical abuse or violence.
- Burnout.
- Alcohol, stimulant and recreational drug abuse.

Some of the previously mentioned factors are briefly explained, taking into account, they may in turn be interconnected and be cause or effect of each other. Liver function is directly or indirectly related to these, which is important to achieve understanding of the exposome, the complexity of pathogenesis and therapeutic approaches. It is also essential to consider the different liver and general responses in men and women.

Exposure and cumulative impact of *irritant agents, insecticides and environment pollutants in water, air and food*, including *heavy metals*, *hormone disruptors*, could be considered a similar group of causal factors of toxicity that initiate an excessive Th2 pattern and/or diminish Th1. Their damage to several organs and systems as immune, endocrine, locomotor, respiratory, lymphatic, neurologic has been demonstrated and related to CFS, hypersensitivity and related conditions, including infertility and cancer.

Chronic exposure to *irritant agents* occurs mainly in working areas or industries, for instance: carpentry, paints, oils, building materials, chemical plants, farming, crops, airports… There is also an exposure at home due to certain ingredients in daily life products (i.e.: clothes, fabrics, hygiene, cosmetics, cleaning). Chronic and intense exposure to *insecticides* such as carbamate and organophosphate are known to provoke inhibition of IL2.

This author would like to highlight that considering first cases of CFS, also named as Myalgic Encephalomyelitis (ME), with or without Fibromyalgia (FBM), were related to some of these agents already in the 80s and 90s. Legislation about for instance insecticides was different throughout the world at that time. People could have been exposed chronically to some of these agents for years, even decades.

Regulatory agencies, such as the World Health Organization (WHO) and European Food Safety Agency (EFSA), study the presence of some of the above-mentioned agents and ingredients [5,6].

Microplastics are undoubtedly a major problem we face globally. They need to be considered as they have shown to stimulate IL6. They can be linked to hormonal disruptors. Still we do not know how to deal with their presence in our bodies. There is so much to learn about their interaction with immune system cells [7] and other systems.

Liver functions are central in this paper. It has been found to have a relevant relationship to CFS and related conditions. Inappropriate liver function is associated with biliary secretion, cholesterol and hormones metabolism, redox regulation, oxidative stress, immunomodulator creation, enzymes such as glutathione peroxidase, superoxide dismutase (SOD), catalases, P450 cytochrome. *Oxidative stress* is considered itself a promoter factor for CFS, chronic or repetitive viral infections, fatigue, allergies, etc., all can be correlated to immune Th1 – Th2 imbalances. Liver is also important for the

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brain, nervous system and emotional balance and wellbeing, and for general energy availability, in general. Excessive oxidative stress can affect *mitochondria* in the liver, hence available energy and detoxification are affected [8]. Liver direct connection to intestine via portal circulation and blood detoxification are an additional link to consider in the intestine - brain relationship. Under high levels of stress, the menstrual cycle is affected: not only ovulation may not happen, but menses may not occur or be dysregulated. Besides the hypothalamus - hypophysis - ovaries axis, liver is also implicated due to its relationship with hormones, carbohydrate. cholesterol metabolism and proper blood flow. Perimenopause and menopause changes also include liver functions modifications. Mitochondria functions diminish, liver ability to deal with oxidative stress is affected as well as immune response. This process is a type of senescence: immune response moves to a lower Th1 and enhanced proinflammatory responses. This also could be considered a reason for the CFS - ME - FBM symptoms and for the chronic viral and recurrent infections in women. On the other hand, functional hyperestrogenism alters thyroid and cortisol function. A special type of obesity, similar to the autoimmune diseases obesity can appear.

Previously acquired viral, bacterial, fungi or parasitic infections may also be trigger factors. Mainly viral conditions such as EBV, HHV, HPV, that promote Th2 excessive response. These viruses can be dormant for years, being activated (with clear symptoms) in specific conditions. An underlying inflammation takes place and modifies the inner milieu. Continuous weak or low level inflammatory situations means extra work for the liver, immune system and metabolism. Inflammation is not effective dealing with these viruses and the system weakens, as a stress response, creating fatigue sensation, hormonal changes and the whole range of symptoms of a "post-viral syndrome".

Recent Covid-19 pandemic was a very clear example, and a factor to trigger already existing CFS and related conditions, or new post viral syndromes related to SARS-CoV-2. Due to previous experience in post viral syndromes, this author proposed this alert about possible EBV, HHV and others viruses, as well as small worms (*Enterobious vermicularis*), reactivations the very first weeks of 2020. Lectures and conferences were dictated at that time both for professionals and the general public. An unpublished, registered document, which is available upon request, compiled this information and was shared with several colleagues to support them. (Lorite-Ayan, N., 2020) This text was also the base for the proposal of using rotavirus vaccine as measure of containment and immune support while Covid vaccines did not exist.

Repetitive *E. coli* infections in the form of chronic or repetitive cystitis (colibacillosis) is also a good example and a frequent case in women. Colibacilosis is usually related to intestinal and liver impairment and can become more complex when other conditions related to liver coexist, such as: myomas, premenstrual syndrome, breast lumps, endometriosis, chronic lumbalgia, anxiety, migraines.

V*accinations* can be a trigger factor in certain individuals because of their mechanism of action, they promote a Th2 reaction. Clinical practice traces some vaccination as a trigger factor for CFS. Certain cases of CFS can be traced back to a trip to another country where specific vaccines were needed. Despite the lack of consensus regarding this point, some authors consider that vaccination acts as an infection and may trigger an anomalous immune response promoting Th1-Th1 imbalance and excessive proinflammatory actions [9].

Inoculated *neurotoxins* and/or microorganisms by vector bites: These cases are more likely to occur in people frequently travelling to tropical o exotic destinations, for pleasure or job, such as airline crew. Dengue disease also can be a promoter of CFS. An increasing number of Lyme disease is also important. Climate change, the movement of invasive species is changing the maps of several diseases.

Any *intestinal impairment* and digestive disorders related to inflammation can both be the cause and consequence of an excessive inflammatory situation or response [10]. Here some can be considered: leaky gut syndrome, microbiota impairment, parasitic conditions, fungi infection, food intolerance, gluten sensitivity, enterocytes damage, loose stool, chronic constipation, diverticulosis, gall bladder conditions. Several nutrients are not properly absorbed. Inflammation persists, intestinal biota and inner enterocytes lining can be altered, Deficient absorption can lead to both physical and

mental fatigue. Low levels of vitamin D have been related to intestinal and gastric impairment. Vitamin D has a crucial role in general health and defence, beyond bones and calcium metabolism.

Digestive disorders include gastritis, hydrochloric acid and/or digestive enzymes insufficiency. Those seem to be opposite situations. Gastric acidity may damage the inner lining of the stomach and create ulcers, on the other hand hypochlorhydria may prevent minerals to be released from food and calcium, magnesium, iron may be affected, thus their functions. Calcium and magnesium manage, among others, muscle relaxation and contraction, iron is key for red cells and haemoglobin creation.

Portal circulation connection between intestine and liver is crucial for both organs, and also for CCS and general health. As long as liver metabolism and enzymes seem to be functionally weakened (this is referred to as "overloaded liver"), CCS would be affected too. Intestinal microbiome is related to other microbiota or flora, such as, lungs, skin, oral, nose. Chronic low grade inflammatory conditions may start here. Leaky gut syndrome highlights that toxins and other pathogens can trespass the intestinal barrier into the bloodstream. Brain, mental and emotions can be affected by the intestine-liver-brain connection.

A*drenal fatigue or adrenal insufficiency* was proposed as a cause of several clinical conditions, including chronic fatigue syndrome and related manifestations, decades ago. This author's clinical experience, case studies and collaboration with colleagues, suggest this adrenal insufficiency appears to be a plausible explanation. Functional and clinical or analytical data often seems not to be correlated. A common case is "functional hypothyroidism". Analytic thyroid hormones data appear to be in range, but manifestations and patient complaints point out a subclinical hypothyroidism. Regarding adrenal hormones such as cortisol, the situation is similar. Analytical data maybe are in range however patient physical symptoms and psychological situation is related to a cortisol insufficiency. On the other hand, a plausible explanation is that long or chronic physiological, mental and/or psychological stress demands high levels of energy, adrenal, cortisol and adrenaline, and kidneys may fail to create enough cortisol. *Mitochondrial implication* is also pointed out as a factor for fatigue and adrenal insufficiency. Mitochondrial dysfunction promotes proinflammatory signalling.

Poor sleep is a major problem in our society. All over the world, statistics show less hours of sleep as a tendency. Sleep problems are referred to as acute or chronic sleep deprivation. Waking hours more than 16 or 18, lead to less than 8 or 6 hours of sleep. Modern society day activity is affected by excessive work and social interaction in social media, smartphones, etc. Pandemic and teleworking revealed that many employees complain about the need of being permanently connected to work or company phones, creating no mental disconnection. Social media, blue light exposure at night, constant scrolling on the apps, affects our brain and sleeping is difficult. During sleep important detoxification and restorative processes take place. Chronic insomnia and few hours of sleep affects CCS and both physical and mental health, and thus affect patients with CFS, inflammatory diseases, in general. Mood, concentration, behaviour may change because of poor sleep [11].

Poor nutrition is related not only to scarce food or diet, but also to a low presence of nutrients. Insufficient intake or absorption of minerals may alter how the elastic tissues in the extracellular matrix work. Selye already proposed the term "acidity", which is not a systemic acidosis, but is related to tiny modifications in fluids pH, oxidative and redox activity. Inflammation processes themselves provoke changes in cells, tissues, also in blood flow, red blood cells, vessels which can lead to poor cellular nutrition, detoxification is slow down, fatigue occurs.

Physical and/or psychological stress are able to create a shift from Th1 to Th2. Some specific activities or works require a high level of physical effort. A common example of this interaction is stress among students during exams and academic effort, where some viruses arise compromising students' results and performance [12]. Elite sport, in general, is a paradigm of how the mind and body processes, injuries, are inextricably linked. In recent years, news has informed top elite athletes who paused or finished their competition because of mental health issues.

Psychological stress, mental overpressure for a long time, stressful or traumatic experiences may affect how the mind deals with daily life and involves CCS and liver functions.

In the 80s, *burnout* was not really considered as a situation to deal with. It was difficult to demonstrate that a person was suffering and indeed going on with hard schedules, long working

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days and weekends, no or almost none personal or family life, were the base for depression, anxiety and physical suffering. Several cases of CFS started. Fatigue, weakness and dull pain, brain fog, inability to take decisions, started and prolonged after what seemed to be *just a flu*. It has been recently that occupational medicine and laboral health care have paid attention to severe fatigue, anxiety, depression, chronic pain and lack of motivation in men and women. Positive Psychology perspective, focused on promoting *Work-Life Balance* (WLB) environments, seemed to impact some companies. Pandemic caused burnout cases to rise up, even to show up. We learnt a lot about telework, work-friendly spaces and mental wellness at work.

Patients of CFS usually refer to one specific situation that seemed to start the intense fatigue sensation, inability to face everyday life, even living in pain. However when going deeper in their story, more factors are found. That event they point out usually was the final straw. They were not feeling well for a long period of time but they forced their minds and pushed forward. On the other hand, patients are found that have been untreated and undiagnosed for years… They went through different specialists with little or small success while the general illness evolved, creating what seemed different conditions.

Still at the time this paper is written there is a large population with no treatment at all and so much frustration. When reading the post patients share in social media groups, as a professional one can feel discouraged. They share which "new illness" has been diagnosed, ask for explanations, compare themselves to others and we know how dangerous it can be. Many get misinformation and partial treatment for individual manifestations, such as anxiety, depression, pain… but the frame involving the complex syndrome itself is untreated. Moreover, side effects of medication such as antidepressant, opiates, are an important part.

5. Women's health challenges and chronic fatigue syndrome: The liver link

The 21st century received past century heritage and started with a flip regarding CFS. More women than men are affected. Our society is facing difficult times, several social and economic crisis, wars, uncertainty, social changes, climate events. Last decades of the past century, over processed food appeared in our lives, additives, preservatives, trans fat, sugar all over… our food was not so nutritious, not so clean so to speak. Pollution in water, air, crops, animals, microplastics… and we humans, in the middle or an *overwhelming progress*.

Prolonged negative experiences can modify our CSS. Amygdala is not the only brain area involved but it is quite important. As mentioned before, even though men also suffer from CFS, this paper aims to highlight women's challenges in our 21st century in a close relationship with what we have and are learning about CFS. Women are more likely to suffer from CFS in all the countries. The Liver Link explains and helps promote global therapeutic approaches to the complex situations related to the base of CFS and all the related conditions as well. It has been explained how the liver is responsible for some of the imbalances affecting CFS.

Liver was the link that united all the different symptoms and apparently different conditions.

Statistics tended to show a profile: Highly educated women, with a professional career. White women beyond their 30s. But we cannot forget, the first women suffering from CFS /ME or post viral syndrome in the 90s, these women were not in their 30s, they were close to their 40 - 45 years old… Upon studying their cases, the imbalances started in their 30s. Some of them got no treatment for more than 10-15 years. They were treated for the isolated conditions: allergies, candida, anxiety, depression, inability to eat almost any food, intestinal cramps, headaches, muscle aches, fatigue. Allergies were surprisingly curious, as these women did not have previous allergies in their adolescence. Allergies patterns have changed in the last decades. Common allergies are no more these responses that would disappear when a young becomes an adult. They are also moving from seasonal to longer periods of time, mainly due to climate change and pollination patterns changes. Some women referred to their candida and intestinal problems as related to prolonged hormonal treatment (hormone replacement therapy for early menopause and/or hormonal contraception for decades). Some of these women had to quit their job, unable to think with clarity, quit their rich intellectual life, some of them told about their need to take one hour to be able to get out of bed and be able to move

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and think. As years go by, more cases are detected, the 21st century is becoming more difficult. Covid pandemic has added new post-viral fatigue cases, and some were already existing CFS in which SARS-CoV-2 may have triggered dormant EBV virus.

There is also a gendered dimension to this issue. Generally speaking, women suffering from CFS refer to their experiences and feelings of desolation, social misunderstanding of their complex situation, becoming isolated from family and friends, not being able to maintain their social life, fear of losing their job, fear of having to choose between personal life and career, fear of not being able to become or to perform as a mother, fear of losing all she had accomplished if she decided to be a mother… Self-expectations of over-achievement, perfectionism, the constant.

A marked gender bias is evident: Life is still different for women and men. Indeed, women still face the extra burden of unpaid domestic and care work, and the social demands of carrying out activities in the formal or informal economy while still delivering in the domestic sphere. The gender pay gap has not been eradicated, and women also face the pressure of gender discrimination, sexual harassment in the work market, and their rights are not protected in the informal sector. That is, the demands of real life are taking a toll in women's health. The gender data is also exacerbated in relation to race and ethnic considerations: in some countries, white women appear to be more likely to suffer CFS but there is no consistency in data on this. Furthermore, other ethnicities may have not been considered due to limitations of each country's health system. There are rising cases in developing countries where gender inequalities are also linked to their specific social contexts, in which women are suffering severely: premenstrual syndrome, polycystic ovaries, endometriosis, poor sexual health, poor menstrual health… Unfortunately, when considered in a broader approach, these "female" conditions are usually mistaken for psychiatric issues. We need to take into account that gynaecological problems of course can occur on their own, that is, not influenced or in relation to CFS; but when CFS is present, treatment and support become more complicated because of the underlying CCS complex situation and other conditions may appear as well.

Feeling unhappy or not motivated at work, negative personal relationships can affect the immune system, psychological and hormonal sphere usually as a cumulative pattern, except for some acute and painful experiences that suddenly provoke an oral dormant herpes virus to flourish.

Sometimes it takes a medium term and the woman starts to feel different, with low or no energy, anxiety, sleep disorders, some pain, enhanced migraine, intestine issues… not feeling "fine", not feeling "sharp".

A shift to Th2 predominance does not happen overnight, it is a cumulative process when we are able to look back and analyse it. It could happen but after an extremely traumatic experience. Post Traumatic Syndrome can be part of a CFS.

Negative situations have the inconvenience of creating negative attitudes in the medium and long term, as if we learn to live emotionally inflamed "by default". Fear, helplessness, frustration, worry, anger… These are related to the liver sphere and affect CCS and liver functions and balance.

Paying attention to these feelings, sensations or negative thoughts is very important. Going on with daily life, similar habits and exhausting activities, pushing beyond limits, suddenly can break anyone. The basic imbalances need to be treated, health can be restored in time, however, *the liver needs to be considered*.

Here we have a list with some of the CFS symptoms and related conditions mentioned in this paper: Fatigue not alleviated by repose or resting, lasting more than 6 months. Fatigue even with apparently no reason.

- Poor concentration. Brain fog. Poor memory.
- Anxiety, depression, helplessness. fear. anger.
- Feeling cheated by society.
- Intestine impairment. Biota damage. Leaky gut syndrome. Bloating. Candida. SIBO. Food intolerance.
- Additives: intolerances or allergies.
- Environmental contaminants reactions.
- Chronic viral conditions, repetitive viral outbreaks: EBV. HHV, CMV, HPV, SARS- CoV-2.
- Pain: Myalgic Encephalomyelitis, headaches, migraines, bones, joints, fibromyalgia.

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- Inability to go easily out of bed or to move, in general.
- Sleep disorders.
- Poor neuromotor coordination.
- Inability to everyday tasks.
- Ovarian cysts. Polycystic Ovaries Syndrome. Myomas.
- Breast lumps. Fibrocystic mastopathy.
- Endometriosis.
- Infertility. Infertility implies an autoimmune factor when we age, but here when CFS is present, it happens sooner.
- Autoimmune conditions: rheumatoid arthritis, multiple sclerosis, thyroiditis, cortisol imbalances.
- Hormonal imbalances.
- Hypothyroidism.
- Metabolic syndrome.
- Diabetes.
- Obesity: difficulty to lose weight.
- Allergies. Several hypersensitivities.
- Oncologic conditions

Fortunately, not all the conditions appear in the same women. Some associations seems more likely to appear one after the other.

Some authors take our attention to the possibility of neurodivergence or psychological entities being hidden because of CFS. This author proposes that liver implication and CFS (understood as a "global systems fatigue") is at the same time a causative factor to be considered in case those psychological entities are diagnosed. Somehow a woman that develops CFS and related conditions already presents an special inner milieu and probably an specific genetic predisposition or epigenetic factors driven by liver functions. Let's not forget the liver is a very powerful and special organ: its functions affect the body and mind. Liver is quite related to brain activity, behaviour and personality.

6. Conclusions

The Liver Link considers liver as a thread in CFS development and in the different changes and conditions that may appear in women's life.

Th2 predominance is linked to EBV, HHV, CMV viruses implication. They can promote and maintain this inflammatory chronic situation. CCS, mainly the immune system, seems unable to correctly cleanse these viruses from the body.

Liver malfunctions support this situation and create the terrain or stress diathesis which promote the evolution of the syndrome with chronic and new conditions. All the factors promote a certain terrain where other viruses such as HPV cannot be eradicated and they prevail in chronic situations.

When specific inflammation flares up, usually due to Th1 immune insufficiency, any mental or emotional situation affecting the immune system, HPV may become a problem too.

Liver consideration as part of the aetiology and therapeutic approaches is key in order to achieve amelioration, longer results and of course, prevent viruses to relapse, a better chronic inflammation control and Th1 - Th2 balance. Thus the liver itself and all the related conditions appear to receive beneficial effects too.

Taking the liver link into account is also a preventive factor both in physical and psychological health.

Liver care can be sustained with healthy habit, for instance clean diet, physical activities, weight control, no alcohol, no trans fats, mindfulness or meditation, specific standardised herbal extracts and specific nutrients, that by the way, will help while there is a pharmaceutical treatment which affects liver metabolism and hepatocytes (i.e.: benzodiazepines, opiates, acetaminophen and others).

Years ago, when this author publicly shared the liver link explanation, a data was proposed: more viruses will join EBV and the herpes family. Neurotropic viruses are more likely to trigger these conditions that have been explained in this paper.

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Liver characteristics is a comprehensive explanation for the complex situation related to CFS.

Liver disharmonies plus chronic viral presence plus chronic inflammation plus external environment plus behaviour and beliefs, all of it, create the inner milieu.

Fortunately, not all the cases evolve the same way, developing the whole range of symptoms or related conditions.

Time and education are important factors to achieve a healthier life.

Women's health has been central in this paper. But of course this author does not forget men.

There is so much to learn about these relationships and conditions.

People are not all the same, each person is unique but they can share similarities in all areas of life: that is why, when describing a disease or a syndrome, biopsychological characteristics of the "group" could also be involved. From this author's experience it is desirable to work in a multidisciplinary way and at the same time, individualising each person's care. This author is well aware of the difficulties this approach means in terms of clinical trials or studies.

CFS and related conditions are increasing amongst the population. Although it is claimed that there is no single specific test for CFS, healthcare professionals and patients need to rely evidence, for instance:

- Compilation of tests, including, viral and immune parameters, brain functions evaluation, hormonal tests, immune status, charts with daily and monthly variability of symptoms, microbiological cultures, parasites presence, etc.
- Psychological evaluation.
- Pain evaluation and score.
- Close observation and records.
- Biological history.

A biological history compiles all that has happened to a person, how and when: by composing a chronological story of a biomedical life, we can approach which imbalances an individual (globally) has suffered and how body and mind have tried to solve those situations and regain balance…or at least, regain the best possible situation. We compose a multidimensional map. Mainly, we deal with a multilayer and 4D puzzle: body, mind, emotions, time.

The 21st century confronts us to a very special and unique health panorama all over the world. The Liver Link consideration can be an exceptional framework in different areas to go on researching and improving people's wellbeing and major understanding also in future threats

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Abbreviations

CCS Central control system
CFS Chronic fatigue syndrome
CMV Citomegalovirus
EBV Epstein Barr Virus
EFSA European Food Safety Agency
FBM Fibromyalgia
HHV Human herpes virus
HPV Human papiloma virus
IFN interferon
IgG Immunoglobulin G
IgM Immunoglobulin M
IL interleukin

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ME Myalgic Encephalomyelitis
NK Natural killer
SIBO Small intestine bacterial overgrowth
SOD Superoxide dismutase
T4 T4 linfocites
T8 T8 linfocites
TFN Tumoral Necrosis Factor
Th1 T cell helper 1
Th2 T cell helper 2
TLL The liver link
WHO World Health Organization

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