Advances in Research

Volume 24, Issue 6, Page 246-258, 2023; Article no.AIR.108460
ISSN: 2348-0394, NLM ID: 101666096

Biological Aspects of Fatigue: A Narrative Review

Maria Paula Carvalho Azevedo [a++], Rafael Francischetto Ultramar [b#], Túlio Novaes Paganini [c++], Elisa Smith Barbiero Medeiros [d*], Catarina Bubach Ribeiro Alves [e] and Hebert Wilson Santos Cabral [f†]

[a] Neurophysiology at Universidade Estadual De Campinas - UNICAMP, Brazil.
[b] SMARTHAIR Clinic LTDA, Brazil.
[c] Digestive System Surgery, Hospital Das Clínicas at UFMG, Brazil.
[d] Medicine at Escola Superior De Ciências Da Santa Casa De Misericórdia De Vitória - EMESCAM, Brazil.
[e] Medicine at EMESCAM, Brazil.
[f] Department of Neurosciences, Science, Technology and Innovations in Mental Health and Quality of Life Research Group at EMESCAM, Brazil.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AIR/2023/v24i61007

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/108460

Systematic Review Article

Received: 23/09/2023
Accepted: 30/11/2023
Published: 09/12/2023

[++] Resident Doctor;
[#] Specialist Doctor;
[†] Post-Doctor and Researcher;
**Corresponding author: E-mail: elisabarbiero@gmail.com;*

ABSTRACT

Introduction: Fatigue is among the most common symptoms in Primary Health-Care and it can be caused by several factors. It is prevailing in the general population and the aggravated condition of fatigue is named Chronic Fatigue Syndrome. This syndrome has a negative impact on the individual's quality of life and it can lead to functional incapacity. Despite decades of research, Chronic Fatigue Syndrome remains a mysterious disease that needs to be highlighted.
Objective: To describe biological aspects of fatigue regarding its definition, biological origin, the main etiologies of Chronic Fatigue Syndrome and its relation with the circadian cycle, as well as the main methods for measurement, diagnosis, complementary tests and treatment.
Method: It is a narrative review, performed from 2019 to 2022, using the PubMed/MEDLINE database and a manual search for studies referred in selected articles from authors with notorious knowledge and specialized groups in the area. It was performed a combination of several search terms added to Fatigue and Fatigue Syndrome, Chronic through Boolean Operators AND, OR and NOT. Scientific articles that involved studies in humans were included in the research. The articles were available in full version for free, in Portuguese, English and Spanish, with no restriction related to the period of publication. The articles were selected by reading of titles and abstracts. The ones that did not fit the aim of this study were excluded. The remaining articles were read in full and selected according to their relevance and contribution to the topic.
Results: Fatigue can be considered peripheral, physical, mental, intellectual and emotional, but there is no consensus regarding its definition. Its main biological origin is related to cytokines, however, fatigue's measurement is still mostly conducted by self-reports of affected patients. There is no objective marker consistently associated to fatigue. Regarding Chronic Fatigue Syndrome, its etiology is still not very well-established, but it was observed that genetic, epigenetic, immunological, infectious, psychosocial, psychiatric and neurological factors can contribute to it. Since fatigue is multidimensional and multifactorial, it is important to associate multiple instruments for its investigation. A potent strategy for the measurement of fatigue is using instruments adapted to the realities, extensively tested in different populations considering socio-economic-cultural aspects. These instruments assess the cognitive function in order to measure several variables and when associated they can increase the accuracy of the investigative instruments. The treatments available include cognitive-behavioral therapy, gradual exercises, immunological treatment, corticosteroids and antidepressants, but they do not guarantee a full remission of symptoms in an isolated way.
Conclusion: Even though there are well-defined biological factors it still lacks a precise marker for the measurement of fatigue. Considering fatigue as multidimensional and multifactorial, it is important to associate several instruments for its investigation. The treatments available have shown effectiveness, but they do not guarantee a full remission of symptoms in an isolated way. For this reason, it is necessary a bio-psycho-social care for these patients.

Keywords: Fatigue; chronic fatigue syndrome; diagnosis; treatment.

1. INTRODUCTION

Fatigue is among the most common symptoms in Primary Health-Care (PHC) [1] and it can be caused by several factors, such as emotional problems, insufficient rest, total absence of physical exercise, inadequate diet, some medications, as well as a chronic condition [2].

Fatigue's symptoms are not specific and are highly subjective, difficult to evaluate, quantify [3] and document in a reliable way [4]. It is prevailing in the general population and it has been described as a state of exhaustion followed by a period of mental or physical effort, a state of reduced ability for work and a low efficiency to respond to stimulus [5].

The aggravated condition of fatigue is named Chronic Fatigue Syndrome (CFS) and its prevalence in the general adult population is of around 0.23% to 2.6% [6,7]. CFS is characterized by persistent or recurrent fatigue, diffuse musculoskeletal pain, sleep disorders and subjective cognitive impairment that lasts six months or more [8]. It has negative impacts on the individual's quality of life and it can lead to functional incapacity [9].

CFS is a complex and debilitating disease of etiology and pathogenesis still unknown, however, its origin is considered multifactorial. The diagnosis is based on at least four symptoms that are mandatory criteria – muscle and joint pain, headaches, cognitive dysfunction and nonrestorative sleep [10]. The available treatments that have shown effectiveness do not guarantee a full remission of symptoms in an isolated way, which demands an especial attention in the management of CFS [11]. The early and comprehensive evaluation, medical management, social and financial support, are factors that can avoid the worsening of the condition associated with the long-term illness [12].

Despite decades of research, CFS still remains a mysterious disease that deserves to be highlighted once public policies aimed at people with CFS are already being proposed. In view of the above, a literature review was conducted with the aim of describing biological aspects of fatigue regarding its definition, biological origin, the main etiologies of CFS and its relation with the circadian cycle, as well as the main methods for measurement, diagnosis, complementary tests and treatment.

2. METHODS

The narrative literature review was conducted in the period from April to June 2022 using mainly the PubMed/MEDLINE database. Considering the exploratory nature of this type of review, different search terms were associated to the descriptors *Fatigue and Fatigue Syndrome, Chronic*, selected in the Medical Subject Headings (MeSH). A manual search was also conducted, including studies quoted in the references of selected articles and institutional sources. The inclusion criterion was the use of original studies, fully available for free, written in Portuguese, English and Spanish, on human species. There was no restriction regarding the publication period of the selected articles.

3. RESULTS AND DISCUSSION

3.1 Definition

From the Latin "*fatigare*", fatigue is reported since Ancient Times, however, its use in the Brazilian Portuguese Language can only be traced until around 1844 [13]. Despite being an old term, there is no consensus among the authors regarding a correct definition of it. Thus, several authors quoted by Mota, Cruz and Pimenta [14] searched for a definition of the term in their own expertise areas such as the following examples: i) in Psychology, Lee and collaborators defined it as "state of exhaustion related to reduced motivation", ii) in Physical Education, McArdie and collaborators presented the definition as "decline in the capacity of generating muscle tension with repeated stimulus", iii) the National Cancer Institute, in Oncology, presented it as "condition characterized by suffering and decrease of functional capacity due to reduction of energy", iv) in Dentistry, Meloncini and collaborators affirmed that "fatigue is referred as 'deterioration' of materials related to partial dentures, usually due to failure in the material itself or the effect of repeated loads".

It was noticed that in the beginning of the 20th century fatigue could not be studied because of its conceptual complexity. Only after the 1950s it became a topic of interest again [15]. However, it is known that in several literature studies fatigue is included as a variable, probably due to its high prevalence in the different populations and due to the harm caused to quality of life. This emphasizes the importance of fatigue's concept to research, mainly regarding studies that produce knowledge applicable to the diagnosis and treatment [14]. Furthermore, this concept is even more important in current times, since it is a recurrent topic in several health-care scenarios.

Mota, Cruz and Pimenta [14] also show that the most highlighted characteristics of fatigue are:

> "Tiredness, exhaustion, weakening, weakness, asthenia, decrease in functional capacity or capacity to perform daily activities, lack of latent resources/ energy/capacity, reduced efficiency to answer to stimulus, discomfort, sleepiness, reduced motivation, aversion to activities, suffering, and desperate need for rest".

Thus, fatigue can be defined as a deep feeling of tiredness, exhaustion and lack of energy [16], which is different from normal experiences of tiredness and sleepiness. Therefore, this phenomenon is a common characteristic of a wide variety of conditions such as chronic inflammatory diseases, infectious diseases, neurological diseases, psychiatric diseases and cancer [17,18].

Fatigue can have peripheral, physical, mental, intellectual and emotional dimensions [19].

Peripheral fatigue is an expression originally used to describe muscle fatigability due to muscle disorders and transmission of impulses in the neuromuscular junction [19]. Physical fatigue can be attributed to a bodily experience of exhaustion followed by a strenuous physical effort. Regarding central or mental fatigue, it is reported as low attention or cognitive blockage, which is usually associated to stress or extended psychic activities [20]. It is subjective, since it is usually self-reported by the individual as a feeling of fatigue [21]. However, this division in dimensions is not universal and it still raises questions about the precision of these terms. Thus, since it is complex to define fatigue, it is even more complex to measure it [3].

As observed, fatigue is a common symptom to several medical conditions and it can be presented in a more acute or chronic form. When there is an extreme fatigue, with defined onset, that persists for at least six months and causes a substantial disorder in the individual, affecting his daily functions, it can be suggested that the patient presents CFS [22], a more serious condition than chronic fatigue itself. This definition by Fukuda and collaborators [22] is the most accepted and internationally known, however, it is not the only one. In Chart 1 is presented the chronology of definitions of CFS and the comparison of their characteristics [23].

3.2 Biological Origin

Pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12 and IL-17, are important in the inflammatory response and essential to the defense against infectious processes and the development of autoimmune diseases. In animals, these cytokines can act on the functioning of the brain during an inflammatory process, causing a pathological behavior [17]. This phenomenon is characterized by sleepiness, loss of appetite, loss of activity and social isolation that results in change in behavior, hypothetically or theoretically, in order to increase survival during the infection. In humans, fatigue can be considered a part of this biological process, triggering a coping mechanism [24,25].

IL-1 is one most well-characterized and studied cytokines, which has an essential role in signaling the behavior of diseases. In this sense, studies show that its intracerebroventricular and intraperitoneal administration induces the pathological behavior in animals. Monocytes and macrophages are the main sources of IL-1 and they produce especially the IL-1β, which has its active form expressed mainly in the surface of monocytes. IL-1 synthesis can be induced by TNF-α/β/g, lipopolysaccharides, virus and antigens [26].

Cytokines produced peripherally can act on the brain from four main ways: activation of the vagus nerve and other nerves through signal to the brain; active and passive transportation through blood-brain barrier; in the circumventricular organs and in the choroid plexus; trough cell secretion in circumventricular organs [27,28].

Chart 1. Definitions of CFS

	CDC 1988	**CDC 1994**	**Comments**
Minimum duration	**6 months**	**6 months**	**6 months**
Functional Damage	Reduction of 50% of the activity	Substantial	Substantial
Cognitive and Neuropsychiatric Symptoms	May be present	May be present	Mandatory
Other Symptoms	6-8 mandatory symptoms	4 symptoms	Not specified
Recent onset	Mandatory	Mandatory	Not mandatory
Medical exclusions	Wide list with physical causes	Clinical importance	Known physical causes
Psychiatric exclusions	Psychoses, Bipolar disorder, drug abuse	Depression, drug abuse, eating disorder, psychoses, bipolar disorder	Psychoses, bipolar disorder, drug use, eating disorder

Source: Wessely et al. ([23])

Other biological agents that interact with processes of the immune system seem to have a similar effect with fatigue. These observations indicate that one of the biological mechanisms of fatigue is early operated by an inflammatory cascade influenced by biological agents that interfere in the signalization of pro-inflammatory cytokines [17].

Moreover, according to Rossi and Tirapegui and Shei and Mickleborough quoted by Vasconcelos [29], one of the processes related to fatigue is serotonin synthesis (5-HT), which is responsible for the regulation of several daily functions, among them the mood and circadian cycle, besides motor activity and cognitive functions. Thus, low production of this neurotransmitter would be related to several symptoms of fatigue, mainly the central one.

3.3 Etiologies

The etiology of CFS is still not well-established. However, some factors can contribute, such as genetic, epigenetic, immunological, infectious, psychosocial, psychiatric and neurological.

Some cases of CFS were described in members of the same family [30], which indicates that familial predisposition and genetic background are possibly associated to CFS. The association of certain genes and people likely to develop the disease in genotyping studies shows point mutations in the DNA or single nucleotide polymorphisms, concluding that some genes can be identified as markers for CFS [31,32]. Although most studies include a small number of patients, some genes were identified in several of them as potential genetic factors inherited and related to CFS [31,33].

Regarding the infectious factors, it is known for decades that chronic fatiguing diseases have been reported after well-documented infections and acute diseases similar to infectious diseases. Despite no agent being identified as the cause of CFS, there are evidences connecting directly or indirectly several chronic infections to the onset and perpetuation of the syndrome, because the symptoms would be related to a disease of the nervous system and the immune response to infection. Most of these infectious agents represent a constant incitement to the immune system, since they are capable of producing a persistent infection often throughout life. The majority of them are also proven to be neuropathogenic [34].

Fatigue is also strongly associated to depression and vice versa. We can establish that there is an overlap in the symptomatology of both diseases. Among the criteria for the diagnosis of depression by the American Psychiatric Association are included: physical fatigue and lack of energy, concentration difficulties and lack of initiative for decision-making. Most part of the instruments and scales used to measure fatigue also include items that are found in the evaluation of other disorders, such as the ones related to mood [35]. Therefore, patients wrongly diagnosed as depressed can actually present chronic fatigue with no depression.

In a study with patients diagnosed with progressive systemic sclerosis, fatigue was present in 67% of the 94 patients being investigated, from which the majority of them was also affected by depression. Considering this, the difference between chronic fatigue and depression is extremely important, particularly when a patient is complaining of fatigue. Researchers believe that detailing the individual's entire history and following the questionnaires is essential to conduct a differential diagnosis of CFS and depressive disorders. Thus, the factors that currently distinguish both pathologies are being the focus of the most varied studies (GRIFFTH, 2008).

Therefore, it is necessary to include mental examination in order to identify abnormalities in mood states, intellectual function, memory and personality, to perform an early diagnosis of CFS. We can highlight specific symptoms such as: depression, anxiety, self-destructive thoughts, and the observation of signs of psychomotor retardation. Even though there is no definitive physical symptom, it is believed that the physical examination can help in the exclusion criteria [36].

CFS can also be associated to other psychiatric disorders, considering that a study proved the increase in prevalence of personality disorders in these patients. This association can happen due to non-compliance with the proposed treatment, manifestation of unhealthy behavior strategies and lack of stable social environment [37].

At last, the encephalon has always been among the etiological hypotheses of disorders related to fatigue. Regarding CFS, the hypotheses also point it out as a possible etiology. The involvement of the central nervous system is suggested by many of the symptoms reported in

CFS, such as difficulties in concentration, attention and memorization. Based on this data, several studies have been conducted to investigate the relation between the central nervous system and CFS by using structural and functional methods of neuroimaging [38]. According to Schwartz RB et al. [39] patients with CFS present brain abnormalities both in the nuclear magnetic resonance and the SPECT (*Single Photon Emission Computed Tomography*) when compared to healthy controls.

The triggering factors of CFS affect the hippocampus leading to neurocognitive deficits and difficulties in the regulation of the stress system and perception of pain. These deficits lead to a substantial decrease in activity and to sleep disorders that, in turn, affect the hippocampus and start a vicious circle of more incapacity [40].

Recently, some researchers have shown that sleep is also an important etiological factor. Studies indicate that patients with CFS presented sleep disorders with a high functional impairment [41,42]. Biologically disturbed sleep is a known cause of fatigue and it can play a part in CFS pathogenesis. However, the nature of the presumed harm of sleep in CFS remains uncertain. Furthermore, primary sleep disorders are frequently detected in patients who are eligible for the diagnosis of CFS. These disorders can contribute to the presence of daytime dysfunction [43].

3.4 The Relation with Circadian Cycle

One of the biggest mysteries of great complexity in current neuroscience is sleep [44]. In 1953, the sleep with Rapid Eye Movement (REM) was identified by Aserinsky and Kleitman [45], introducing the understanding of sleep. In 1998, the discovery of hypothalamic peptides, hypocretins and their roles in the sleep-wake cycle and in the pathophysiology of narcolepsy (cataplexy) resized the hypothalamus in controlling the sleep-wake cycle, previously attributed only to structures located in the brainstem and thalamus. Currently, the control of this cycle is attributed to hypothalamic systems and their respective functional interactions with the circadian control temporization system [46,47].

Homo sapiens is a daytime species adapted to perform activities in a light phase of the light/dark cycle and rest in the dark phase [48]. Therefore, the main sleep period is in the dark phase, despite happening in other moments of rest during the day. The system that controls behaviors related to sleep is complex and it relies on several elements [49,50]. In mammals, chronobiological coordination is in the suprachiasmatic nucleus of the hypothalamus, located along the optic nerve. In this region, retina connections inform the system about the existence of light. Obeying the stimulus of the suprachiasmatic nucleus in the absence of light, melatonin is secreted by the pineal gland translating the photic information into chemical stimulus to all cells. The exposure to light interacts with the suprachiasmatic nucleus and it can change the clock cycles. Therefore, intense light in the late afternoon turns the clock back and, on the other hand, intense light in the early morning sets the clock forward [51,52].

Besides melatonin, Pinato [53] affirms there are variations on the levels of 5-HT throughout the circadian cycle, which indicates that changes caused in this cycle can influence on the symptoms of fatigue due to the decrease of 5-HT concentration. In this sense, a study [54] compared patients with polio and concluded that fatigue varies according to the circadian cycle. Moreover, it can present a progressive worsening or in some time of the day. This is due to the poor sleep quality in these patients, which indicates that sleep disorders must be considered in the research and treatment of fatigue [55].

3.5 Fatigue Measurement

Currently, there are a variety of instruments to assess or conduct the measurement of fatigue and most of these instruments are based on self-report of symptoms. Chart 2 shows the most used scales in the world and their authors [17].

Some scales were designed for specific diseases, while others were used as a generic instrument for a larger number of diseases. It can be highlighted that some tests try to measure several aspects or domains of fatigue, while others “force” the individual to describe fatigue as a unique measure (single dimension), such as the visual analogue scale (VAS), but this measure is still open for discussion. However, it is important to emphasize that all scales are based on self-report and it is essential to acknowledge the importance of the information derived from the question asked.

Many of the studies that approach measurement of fatigue are reviews [56]; GERBER, 2019; MACHADO, 2021 that focus on eliciting and evaluating the different tools available. However, they all reach similar conclusions and approach the absence of scales and questionnaires able to evaluate fatigue in a multidimensional and standardized way, which would help in the diagnosis and comparison of scientific studies on the topic. Thus, the prevalence of the fatigue reported is influenced by the types of measurement tools, and the results based on the use of different scales cannot be easily compared [17]. In this way, it is important for researchers to focus on the topic in order to create a new tool for this purpose.

Therefore, reliable quantification and identification of abnormal levels of fatigue in clinical and general populations are important to develop early intervention plans and evaluate the effectiveness of the treatments (CELLA, 2010).

3.6 Diagnosis and Complementary Tests

Diagnosis of CFS is a challenge for health-care professionals for several reasons. One of the most important gaps is the presence of fatigue in a large number of disorders. However, currently there are at least four main symptoms that are mandatory for the diagnosis: muscle and joint pain, headaches, cognitive dysfunction and nonrestorative sleep [10]. Chart 3 shows the criteria for diagnosis of CFS according to the Centers of Disease Control and Prevention (CDC) [36].

Furthermore, there is no proper laboratory routine that is directed to the condition, mostly because of its multifaceted symptomatology which makes the diagnosis even more challenging. Changes in the levels of immunoglobulins, inflammatory cytokines and lymphocytic load are commonly reported as conditions associated with CFS. Moreover, the deficiency of some nutrients, such as vitamin B and C, sodium, magnesium, zinc and coenzyme Q10 seem to be related to severe cases of the syndrome (BJORKLUND, 2019).

3.7 Treatment

It is estimated that only 5% (that is, average rate of full recovery) of patients with CFS recover naturally. Thus, the search for a curative treatment for CFS should be considered. The treatments available demonstrated effectiveness, but they do not guarantee full remission of symptoms in an isolated way. Therefore, in order to promote a better quality of life it is necessary a bio-psycho-social care of these patients [11].

Chart 2. Fatigue measurement scales

Scale Name	References	Dimensions	Comments
"Chalder Fatigue scale" "Fatigue assessment instrument"	Chalder et al. (1993) Schwartz et al. (1993)	Physical fatigue, mental, severe, specific situations, consequence of fatigue.	Generic
"Fatigue Impact Scale (FIS)"	Fisk et al. (1994)	Physical, cognitive, psychosocial fatigue.	Generic
"Fatigue Severity Scale (FSS)"	Krupp et al. (1989)	Only dimension.	Generic
"Multidimensional Fatigue Inventory (MFI-20)"	Smets et al. (1995)	General, mental, physical fatigue, reduction of motivation, reduction of activity.	Generic
"The piper fatigue scale"	Piper et al. (1989) Piper et al. (1998)	Behavioral, severity, affection, sensor, mood/cognitive.	Generic
"Visual Analogue Scale (VAS)" "Medical outcomes study short form"	Ware et al. (1983)	Only dimension. Vitality, evaluate and fatigue	Generic/Heatth-Related Quality Of Life (HRQOL)
"Parkinson fatigue scale"	Brown et al. (2005)	Physical fatigue.	Parkinson's disease
"Profile of fatigue"	Browman et al. (2004)	Somatic fatigue, mental and overall discomfort.	pSS

Source: Norheim et al.[27]

Chart 3. Criteria for CFS

Criteria for Chronic Fatigue
1. Unexplained and persistent fatigue, which is not due to continuous effort and it is not substantially relieved by rest. It has a new onset (not throughout life) and results in significant decrease in the levels of activity.
and
2. Four or more symptoms are present for 6 or more months and include:
♣Memory or concentration disorders ♣Extreme malaise, prolonged exhaustion and exacerbated symptoms after physical or mental effort ♣Poor sleep quality ♣Muscle pain ♣Headaches with no severity ♣Joint pain with no swelling or redness ♣Frequent or recurring sore throats ♣Tensions in cervical or axillary lymph nodes ♣New or aggravated types of headaches

Source: CDC[46]

Thus, some fundamental principles can be considered in the management of these patients, based on this need: a) develop an individualized management plan for physical and social rehabilitation ; b) discourage excessive rest and minimize social isolation; c) keep a regular contact; d) evaluate the origin of any new symptom or deterioration of function; e) provide support for the person and his family, including access to social security, educational assistance and rehabilitation services, when necessary. The primary objectives are focused on relieving the symptoms and maximize functional capacity, as well as most of the treatments. In addition, it can be developed a clear and mutual understanding around the nature of the problem and more realistic expectations regarding the possibilities of outcome in the long-term (WORKIN GROUP OF THE ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS, 2002). For the treatment, the following methods can be considered: Cognitive-behavioral Therapy (CBT), Therapy with Gradual Exercises (TGE), immunological treatments, corticosteroids and antidepressants.

In this sense, it can be observed the difficulty to define and diagnose CFS due to the presence of an anatomo-physiological substrate and the absence of a biological pattern to be considered as causative agent of this pathology. Several treatments, including CBT and TGE were proven effective for the reduction of fatigue. Therefore, reliable quantification and identification of abnormal levels of fatigue in clinical and general populations are important to develop early intervention plans and evaluate the effectiveness of the treatments (CELLA, 2010). There are several debates and dilemmas that make the acceptance of the disease more difficult for the patients' peers, family members, colleagues, doctors and health plans [57].

4. CONCLUSION

Based on the above considerations, it was verified that there is no consensus among the references and researchers regarding a correct definition of the term fatigue. This shows the importance of the discussion on the topic, as well as further continuous and solid scientific research. Thus, it is possible to normatize this entity that is largely discussed in current times and brings relevant impacts on the bio-psycho-social and socioeconomic point of view. It must be emphasized that fatigue is related to some biological aspects and the most relevant ones are the cytokines and all their chain of actions, among other inflammatory cascades. The etiology of CFS is still not well-established. However, some factors can contribute, such as genetic, epigenetic, immunological, infectious, psychosocial, psychiatric and neurological. It was observed that fatigue presents a well-defined circadian variation and poor sleep quality is associated with fatigue, therefore, sleep disorders should be more well-evaluated and treated. It is important to mention the absence of an objective marker consistently associated to fatigue. This is perhaps one of the most challenging areas for further research. It is also highlighted that the main objective of laboratory investigation is to exclude other conditions that can cause fatigue and the recommended tests for initial evaluation are: blood test, VSG, TSH, electrolytes (sodium, potassium, calcium and

phosphate), transaminases and urine test (protein, blood and glucose). It can also be noted that the primary objectives of treatment are to relieve symptoms and maximize patients' functional capacity. The available treatments, including CBT and TGE, highlighted effectiveness, but they do not guarantee a full remission of symptoms in an isolated way. This corroborates the real need for better concept, screening and early identification, which are essential for diagnosis interpretation and, consequently, therapeutic effectiveness. Therefore, it is notable the need for more research in the specific area in order to better define the proper treatment. There are several debates and dilemmas that make the acceptance of the disease more difficult for the patients' peers, family members, colleagues, doctors and health plans.

In the last years, it was observed that the topic of fatigue is part of pillars related to prevention in several companies in Brazil and around the world. This proves the need for knowledge and management along with workers from different areas, not only due to the severe biological impacts that affect labor activities, but also for the high association with risk of accidents that bring intangible and irreversible losses for different population groups. It is also emphasized the strong academic impact for organizations and for the society, which encourages the need for research investments and the need to bring academia closer to industry. Thus, it is necessary to develop methodologies of short and objective application, such as technological tools for screening with scientific basis. They can optimize the early identification and be one of the pillars of the effective therapeutic process and a basis for the promotion of preventive actions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Zimmer PM, Lima AK. Tiredness or fatigue. In: Duncan BB, Schmidt MI, Giugliani ERJ, eds. Outpatient medicine: evidence- based primary care practices. 3rd ed. Porto Alegre: Artmed. 2004;1151- 6.
2. Care for chronic conditions in primary health care: the imperative of consolidating the family health strategy. / Eugênio Vilaça Mendes. Brasília: Pan American Health Organization. 2012;512.
3. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of neurology. 1989;46(10):1121-3.
   Available:https://www.ncbi.nlm.nih.gov/pubmed/2803071
   [Accessed on Dec 12 2018]
4. Persson PB, Bondke Persson A. Fatigue. Acta Physiol (Oxf). 2016;218(1):3-4.
   DOI: 10.1111/apha.12756.
   PMID: 27428862
5. Health Sciences Descriptors: DeCS [Internet]. 2017 edition. São Paulo (SP): BIREME/PAHO/WHO; 2017
   Available:http://decs.bvsalud.org/I/homepagei.htm
   [Accessed on May 18, 2017; quoted on June 13, 2017]
6. Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-sectional polysomnography analysis. BMJ open. 2013;3(6):53-73.
   Available:https://bmjopen.bmj.com/content/3/6/e002999
   [Accessed on Feb 18, 2019]
7. Wessely S. Chronic fatigue syndrome: A 20th century illness?. Scandinavian Journal of Work, Environment & Health. 1997;23(3):17-34.
   Available:https://www.ncbi.nlm.nih.gov/pubmed/9456063
   [accessed on Feb 18, 2019]
8. DeCS Síndrome da Fadiga Crônica (inserir)
9. STRASSHEIM VJ, et al. Defining the prevalence and symptom burden of those with self-reported severe chronic fatigue syndrome/ myalgic encephalomyelitis (CFS/ME): A two-phase community pilot study in the North East of England. BMJ Open. 2018;8(8).
10. Carruthers BM, Van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles AP, Speight N, Vallings R, Bateman L. Myalgic encephalomyelitis: international consensus criteria. Journal of internal medicine. 2011;270(4):327-38.
    Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3427890/
    [Accessed on Feb 04, 2019]

11. Whiting P, Bagnall AM, Sowden AJ, Cornell JE, Mulrow CD, Ramírez G. Interventions for the treatment and management of chronic fatigue syndrome: A systematic review. Jama. 2001;286(11):1360- 8.
Available:https://www.ncbi.nlm.nih.gov/pubmed/11560542
[Accessed on Jan 22, 2019]
12. Brenna E, Gitto L. The economic burden of Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME): An initial summary of the existing evidence and recommendations for further research. European Journal for Person Centered Healthcare. 2017;5(2):412-420.
13. Da Cunha AG. Dicionário etimológico da língua portuguesa. São Paulo: Lexikon Editora; 2019.
14. Corrêa de Faria Mota DD, Lopes Monteiro da Cruz DD, Andrucioli de Mattos Pimenta C. Fadiga: uma análise do conceito. Acta Paulista de Enfermagem [periódico na internet]. 2005;18(3):285-93.
Available:http://www.scielo.br/scielo.php?pid=S010321002005000300009&script=sci_abstract&tlng=pt
[Accessed Feb 23, 2019]
15. Nail LM, Winningham ML. Fatigue and weakness in cancer patients: the symptom experience. Semin Oncol Nurs [periódico na internet]. 1995;11(4):272-8.
Available:https://www.ncbi.nlm.nih.gov/pubmed/8578035
[Accessed on Jan 15, 2019]
16. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. Current opinion in neurology [periódico na internet]. 1996;9(6):456-60.
Available:https://www.ncbi.nlm.nih.gov/pubmed/9007405 Dec
[Accessed on Feb 22, 2019]
17. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. Rheumatology [periódico na internet]. 2011;50(6):1009-18.
Available:https://www.ncbi.nlm.nih.gov/pubmed/21285230
[Accessed on Feb 25, 2019]
18. Hewlett S, Cockshott Z, Byron M, Kitchen K, Tipler S, Pope D, Hehir M. Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. Arthritis Care & Research [periódico na internet]. 2005;53(5):697-702.
Available:https://www.ncbi.nlm.nih.gov/pubmed/16208668
[Accessed on Feb 08, 2019]
19. Chaudhuri A, Behan PO. Fatigue in neurological disorders. The lancet. 2004; 363(9413):978-88.
Available:https://www.ncbi.nlm.nih.gov/pubmed/15043967
[Accessed on Jan 23, 2019]
20. DECSb adiga mental.
Available:https://decs.bvsalud.org/ths/resource/?id=5326&filter=ths_termall&q=fadiga%20mental#Concepts
21. Berrios GE. Feelings of fatigue and psychopathology: A conceptual history. Comprehensive psychiatry [periódico na internet]. 1990;31(2):140-51.
Available:https://www.ncbi.nlm.nih.gov/pubmed/2178863
[Accessed on Mar 18, 2019]
22. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: A comprehensive approach to its definition and study. Journal Of Chronic Fatigue Syndrome. 1995;1(2):67-84.
Available:https://www.ncbi.nlm.nih.gov/pubmed/7978722
[Accessed on Jan 23, 2019]
23. Wessely S, Sharpe M, Hotopf M. Chronic fatigue and its syndromes. Oxford: Oxford University Press; 1998.
24. Hart BL. Biological basis of the behavior of sick animals. Neuroscience & Biobehavioral Reviews [periódico na internet]. 1988;12(2):123-37.
Available:https://www.ncbi.nlm.nih.gov/pubmed/3050629
[Accessed on Jan 22, 2019]
25. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain, behavior, and immunity [periódico na internet]. 2007;21(2):153-60.
Available:https://www.ncbi.nlm.nih.gov/pubmed/17088043
[Accessed on Mar 18, 2019]
26. Dinarello CA. The IL-1 family and inflammatory diseases. Clinical and experimental rheumatology [periódico na internet]. 2002;20(5;Suppl27):S1-13.
Available:https://www.ncbi.nlm.nih.gov/pubmed/14989423
[Accessed on Feb 25, 2019]
27. Maier SF. Bi-directional immune–brain communication: Implications for understanding stress, pain, and cognition.

Brain, behavior, and immunity [periódico na internet]. 2003;17(2):69-85.
Available:https://www.ncbi.nlm.nih.gov/pubmed/12676570
[Accessed on Jan 12, 2019]

28. Quan N, Banks WA. Brain-immune communication pathways. Brain, behavior, and immunity [periódico na internet]. 2007;21(6):727-35.
Available:https://www.ncbi.nlm.nih.gov/pubmed/17604598
[Accessed on Mar 03, 2019]
29. Vasconcelos, Carla Aparecida de. Fadiga e sonolência em aviadores: análise de variações da voz, fala e linguagem. 2019. 355 f. Dissertação (Mestrado) - Curso de Neurociências, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, 2019.
Avaliable:https://acesse.dev/repositorioufmg184333969
30. Endicott NA. Chronic fatigue syndrome in private practice psychiatry: Family history of physical and mental health. Journal of Psychosomatic Research [periódico na internet]. 1999;47(4):343-54.
Available:https://www.ncbi.nlm.nih.gov/pubmed/10616228
[Accessed on Feb 19, 2019]
31. Saiki T, Kawai T, Morita K, Ohta M, Saito T, Rokutan K, Ban N. Identification of marker genes for differential diagnosis of chronic fatigue syndrome. Molecular Medicine [periódico na internet]. 2008;14(9-0):599-607.
Available:https://www.ncbi.nlm.nih.gov/pubmed/18596870
[Accessed on Mar 03, 2019]
32. Gow JW, Hagan S, Herzyk P, Cannon C, Behan PO, Chaudhuri A. A gene signature for post-infectious chronic fatigue syndrome. BMC medical genomics [periódico na internet]. 2009;2(1):38.
Available:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2716361/
[Accessed on Jan 25, 2019]
33. Fang H, Xie Q, Boneva R, Fostel J, Perkins R, Tong W. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. Pharmacogenomics [periódico na internet]. 2006;7(3):429-40.
Available:https://www.ncbi.nlm.nih.gov/pubmed/16610953
[Accessed on Feb 18, 2019]
34. Komaroff AL, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. 2011;31(03): 325-337.
Available:https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0031-1287654
[Accessed on Jan 22, 2018]
35. Jacobsen PB, Donovan KA, Weitzner MA. Distinguishing Fatigue and Depression in. Semin Neurol. 2003 8(4):229-240.
Available:http://www.cas.usf.edu/~jacobsen/fatigue%20&%20depression.pdf
[Accessed on Dec 26, 2018]
36. Public Health Service, US Centers for Disease Control and Prevention (CDC). Syndrome CF. Atlanta: National Center for Infectious Disease; 1998.
37. Nater UM, Jones JF, Lin JM, Maloney E, Reeves WC, Heim C. Personality features and personality disorders in chronic fatigue syndrome: A population-based study. Psychother Psychosom. 2010 79(5):312-8.
Available:https://www.karger.com/Article/Abstract/319312
[Accessed on Dec 27, 2018]
38. Ortega F, Zorzanelli R. Neuroimaging and the case of chronic fatigue syndrome. Cien Saude Colet. 201116(4):2123-32.
Available:http://www.scielo.br/scielo.php?pid=S141381232011000400012&script=sci_arttext&tlng=pt
[Accessed on Dec 27, 2018]
39. Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. AJR. 1994;162(4):935-41.
Available:https://www.ajronline.org/doi/abs/10.2214/ajr.162.4.8141020
[Accessed on Dec 28, 2018]
40. Saury JM. The role of the hippocampus in the pathogenesis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Med Hypotheses. 2016:30-8.
Available:https://www.sciencedirect.com/science/article/pii/S0306987715004478
[Accessed on Dec 29, 2018]
41. Morriss R, Sharpe M, Sharpley AL, Cowen PJ, Hawton K, Morris J. Abnormalities of sleep in patients with the chronic fatigue syndrome. BMJ. 1993:306(6886):1161-4.
Available:https://www.bmj.com/content/306/6886/1161.short
[Accessed on Dec 29, 2018]

42. Morriss RK, Wearden AJ, Battersby L. The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome. J Psychosom Res. 1997;42 (6):597-605.
Available:https://www.sciencedirect.com/science/article/pii/S0022399997898959
[Accessed on Dec 29, 2018]
43. Mariman AN, Vogelaers DP, Tobback E, Delesie LM, Hanoulle IP, Pevernagie DA. Sleep in the chronic fatigue syndrome. Sleep Med Rev. 2013;17(3):193-9.
Available:https://www.ncbi.nlm.nih.gov/pubmed/23046847
[Accessed on Dec 30, 2018]
44. Rechtschaffen A, Bergmann BM. Sleep deprivation in the rat: an update of the 1989 paper. Sleep: Journal of Sleep and Sleep Disorders Research. 2002;25(1): 18-24.
Available:https://psycnet.apa.org/record/2002-12712-004
[Accessed on Dec 30, 2018]
45. Aserinsky E, Kleitman N. Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. Neuropsychiatry Clin Neurosci. 2003;15(4): 454-5.
Available:https://pdfs.semanticscholar.org/242c/d7cd847764f5eb5e90ffa0f3372c49062646.pdf
[Accessed on Jan 2, 2019]
46. Pace-Schott EF, Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci. 2002;3(8):591.
Available:https://www.nature.com/articles/nrn895
[Accessed on Jan 3, 2019]
47. Alóe F, Azevedo AP, Hasan R. Sleep-wake cycle mechanisms. Braz J Psychiatry. 2005 May 27:33-9.
Available:http://www.scielo.br/scielo.php?pid=S151644462005000500007&script=sci_arttext&tlng=es
[Accessed on Jan 4, 2019]
48. Arendt J. Melatonin and human rhythms. Chronobiol Int. 2006;1(1-2) :21-37.
Available:https://www.tandfonline.com/doi/abs/10.1080/07420520500464361
[Accessed on Jan 17, 2019]
49. Herzog ED, Schwartz WJ. Invited Review: A neural clockwork for encoding circadian time. J Appl Physiol. 2002;92(1) :401-8.
Available:https://www.physiology.org/doi/abs/10.1152/japplphysiol.00836.2001
[Accessed on Jan 13, 2019]
50. Mauk MD, Buonomano DV. The neural basis of temporal processing. Rev Neurosci. 2004;27:307-40.
Available:https://www.annualreviews.org/doi/abs/10.1146/annurev.neuro.27.070203.144247
[Accessed on Jan 15, 2019]
51. Hastings MH, Herzog ED. Clock genes, oscillators, and cellular networks in the suprachiasmatic nuclei. J Biol Rhythms. 2004;19(5):400-13.
Available:https://journals.sagepub.com/doi/abs/10.1177/0748730404268786
[Accessed on Jan 11, 2019]
52. Scheer FA, Czeisler CA. Melatonin, sleep, and circadian rhythms. Sleep Med Rev. 2005;9(1):5-9.
Available:https://www.sciencedirect.com/science/article/pii/S108707920400111X?via%3Dihub
[Accessed on Feb 12, 2019]
53. Pinato L. Sistema serotonérgico - relações com o sistema de temporização circadiano [Doutorado]. Instituto de Ciências Biomédicas da Universidade de São Paulo - USP; 2007.
Available:https://www.teses.usp.br/teses/disponiveis/42/42131/tde-31012008-105920/publico/LucianaPinato_Doutorado.pdf
54. Viana CF, Pradella-Hallinan M, Quadros AA, Marin LF, Oliveira AS. Circadian variation of fatigue in both patients with paralytic poliomyelitis and post-polio syndrome. Arq Neuropsiquiatr. 2013;71(7):442-5.
Available:http://www.scielo.br/scielo.php?pid=S0004282X2013000700442&script=sci_arttext&tlng=es
[Accessed on Dec 19, 2018]
55. Martinez D, Lenz MD. Circadian rhythm sleep disorders. Indian J Med Res. 2010;131(2):41-149.
Available:https://www.ncbi.nlm.nih.gov/pubmed/20308739
[Accessed on Dec 20, 2018]
56. Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. Am J Hosp Palliat Care. 2014;31(5):562-75.
DOI: 10.1177/1049909113494748
[Accessed on 2013 Jul 26]
PMID: 23892338.

57. Wessely S. Neurasthenia and fatigue syndromes. In G. Berrios & R. Porter. A history of clinical Psychiatry: the origins and history of psychiatry disorders. London: The Athlone Press. 1995;509-32.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/108460