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Chronic Fatigue Syndrome – Latest Evidence on a Complex Disorder

Recent publications on triggers, symptoms, biomarkers, treatment and its association with post-COVID

Myalgic encephalomyelitis (ME), better known as the **Chronic Fatigue Syndrome** (CFS) is a neuroimmunological multisystem disease affecting millions of people worldwide. The global prevalence of CFS ranges between 0.4% and 2.5% and is growing.[1] **This very complex disorder is characterized by severe heterogeneous symptoms affecting the patients' cognitive, autonomic and neuropathic function**[2,3]. Clinical guidance has been rare, or even potentially harmful. Thus, up to 91% of patients in the United States remain undiagnosed or even misdiagnosed with e.g. depression. Those diagnosed often do not receive appropriate treatment[1].

Disease patterns, symptoms and impairments

Chronic Fatigue (CF) is defined as a "substantial fatigue lasting for more than 6 months" [4] and is one of the most significant health problems in such patients. But also impaired concentration and short-term memory, pain, ineffective sleep, exercise intolerance and an affected cardiovascular system are possible signs for ME/CFS.[5] All of them significantly **decrease the patients' quality of life.**

One of the hallmark parts of the mechanism underlying the pathology of CFS is a **dysfunction of the autonomic nervous system (ANS)**. In up to 95% of those with ME/CFS, prolonged standing or sitting will cause or worsen symptoms. According to the NAM diagnostic criteria (2015)[6], one manifestation is **orthostatic intolerance**, which includes orthostatic hypotension, postural orthostatic tachycardia syndrome, and neurally mediated hypotension.

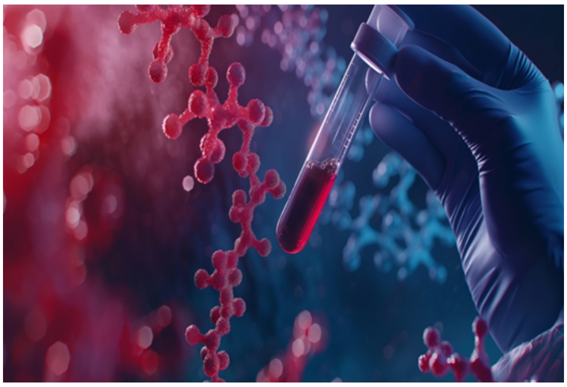
Accurate identification of orthostatic intolerance avoids misdiagnosis with a psychiatric disorder and ensures its appropriate management, which is different from that of anxiety.[1]

Post-exertional malaise (PEM) is also a very typical impairment for CFS patients, which causes a substantial deterioration of symptoms being provoked in response to physical exercise. This symptom is often not mentioned immediately as patients may not be familiar with the concept.[1] In a recent study by Kujawski et al. the differences in CFS patients with and without this kind of exercise intolerance were investigated by means of indicators of aortic stiffness, autonomic nervous system function, blood pressure and severity of mental and physical fatigue. Higher mental fatigue and sympathetic activity in rest are related to an increased risk of PEM, while higher central systolic blood pressure is associated with a reduced risk of PEM.[7]

A series of further highly interesting studies have been published during the past five years also using **autonomic function testing** to explore and better understand CFS in terms of possible triggers, effective biomarkers, associations with post-COVID conditions as well as treatment approaches to alleviate the suffering:

Triggers

Infection is reported as most common trigger for CFS. Kristiansen et al. investigated fatigued and non-fatigued adolescents who had suffered from the **Epstein-Barr-Virus** (EBV) 6 months after infection in terms of clinical symptoms and markers of disease mechanisms. Autonomic activity was assessed through continuous, noninvasive monitoring of cardiovascular variables during supine rest, controlled breathing and upright standing.



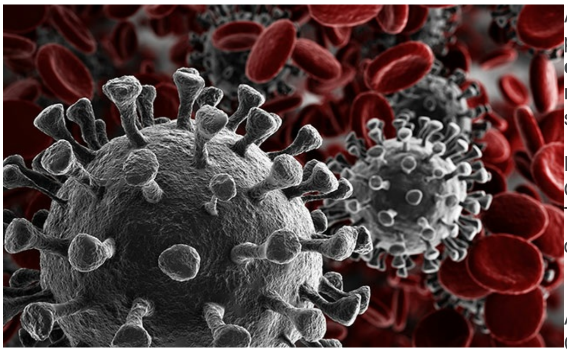
The group with chronic fatigue symptoms had significantly higher scores for all clinical symptoms than those without CF. All markers of infection and most immune, neuroendocrine and autonomic markers were similar across both groups.[4]

New biomarker

Anzcue et al. describes the investigation of Plasma Neurofilament light chain (NfL) as a new biomarker to more specifically diagnose CFS in association with neurological dysfunctions.Increased NfL levels in the patients' blood may indicate neuroaxonal damage causing cognitive dysfunction and autonomic impairment.[2] This biomarker has already been used in patients with multiple sclerosis to identify individuals at risk for future disease activity. [8]

CFS and post-COVID-19

Another important aspect of ME/CFS is that studies showed that **ME/CFS and post-Covid 19 sufferers have similar symptoms and appear to be closely related**. One review even suggested that the number of cases of ME/CFS could double as a result of the pandemic. [1] In their systematic review, Wong et al. (2021) found a broad overlap of both diseases and concluded that early investigations into long COVID symptomatology suggest **many overlaps with clinical presentation** of ME/CFS. [9]



A recent study by Azcue et al. compared the symptoms in post-COVID patients and patients suffering from ME/CFS. Both present similarities such as **fatigue, cognitive problems, brain fog, cardiovascular events, autonomic and neuropathic symptoms**. Both patient groups presented a higher heart rate in supine and standing position compared the healthy controls.

Both syndromes showed a much higher number of patients with Postural Orthostatic Tachycardia Syndrome (POTS) than expected in the healthy population. They were much more sensitive to hot stimuli, suggesting small-fiber neuropathy, a disease of the tiny nerve fibers, which are mainly located under the skin.[3]

A several studies report chronic fatigue as one of the main discomforts for the post-COVID-19 syndrome, as for example the Viennese group around Ludwig et al. which detected CF in 77,6% of their COVID-19 study population.[10] Chung et al. explored the **underlying pathophysiology of the post-COVID-19 syndrome associated with autonomic dysfunction such as POTS**. This study showed that clinical features and the results of the autonomic function tests showed no difference between patients with POTS and the post-COVID-19 syndrome. The results suggest **vasomotor dysfunction, which may be the reason for chronic fatigue or orthostatic intolerance**.[11]

Therapy approaches

Although there is no overall medication available yet for ME/CFS, symptoms can be alleviated individually. The study of Kujawski et al. introduces an Individual Activity Program (IAP) for chronic fatigue patients based on cardiovascular, mitochondrial and fatigue parameters. They concluded that – even though exercise was not well accepted by more than the half of the study population – **the therapeutic effects of IAP were a reduction of fatigue and the improvement of the functional performance** with an impact on autonomic and mitochondrial function. [5]

As shown in the cited studies, **including autonomic function testing in the diagnosis path for patients with suspected CFS has become a supporting objective aspect** apart from the standard methods based on patient history, blood markers or subjective answers to questionnaires. "The passive standing or tilt table tests can objectively confirm orthostatic intolerance" [1], which is an characteristic aspect of CFS. Lapp et al. already stated in 2003 that **tilt table testing is recommended "in the majority of persons with CFS/ME/FM, especially when fainting, flushing, and postural frailty are present."**[12] This might contribute to also guide treatment decisions in order to bring patients back to normal life again.

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