**Epstein-Barr virus and the origin of myalgic encephalomyelitis or chronic fatigue syndrome**

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**Supplemental Table 1.** Diagnostic criteria for Chronic Fatigue Syndrome or Myalgic Encephalomyelitis.

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| Criteria | Main | Minor |
| Holmes, 1988. (1) | ≥ Six months of severe chronic fatigue not due to exertion or other illness and which reduces or affects the activity of daily life by less than 50%. | ≥ Eight of the eleven minor symptoms:   * Fever or chills * Sore Throat * Tender lymph nodes * Muscle weakness * Muscle pain * Post-exertional malaise * Headaches * Migratory Arthralgia * Neuropsychiatric complaints * Sleep disturbances * Sudden onset of symptoms |
| Fukuda Criteria, 1994.(2) | ≥ Six months of severe chronic fatigue not due to exertion or other illness and which interferes with daily life | ≥ Four of the following eight symptoms:   * Sore throat * Tender cervical or axillary nodes * Muscle pain * Joint pain * Post-exertional malaise lasting more than 24 hours * Headaches * Impaired short-term memory or concentration * Unrefreshing sleep |
| Canadian Consensus Criteria for ME, 2003.(3) | ≥ Six months of:   * Persistent, unexplained, new-onset fatigue that reduces activity level, and/or * Post-exertional malaise, and/or * Sleep dysfunction and/or * Pain in the form of myalgia / generalized arthralgia or headaches | * ≥Two neurological/cognitive symptoms * Confusion * Impaired concentration and short-term memory * Difficulty in processing information, categorizing and retrieving words * Perceptive and sensory alterations * Ataxia * Muscle weakness * Fasciculations   and ≥ one of two of the following categories:   * Autonomic : orthostatic intolerance, PoTS, nausea, irritable bowel syndrome, urinary frequency, palpitations, stress dyspnea * Neuroendocrine: loss of thermostatic stability, weight change * Immunological: painful lymph nodes, recurrent sore throat, general malaise, food/drug sensitivity |
| International Consensus Criteria for ME (ME-ICC), 2011. (4) | Post-effort neuroimmune exhaustion with marked and prolonged post-effort physical or cognitive fatigue with a prolonged recovery period | ≥ A symptom of three of these categories:   * Neurocognitive impairment * Pain * Sleep disturbances * Neurosensory, perceptual and motor disorders   ≥ A symptom of three of these categories:   * Flu-like symptoms * Susceptibility to viral infections * Gastrointestinal Tract Symptoms * Genitourinary symptoms * Sensitivities   ≥ A symptom of these categories:   * Cardiovascular * Respiratory * Loss of thermostatic stability * Intolerance to extreme temperatures |

**Supplemental Table 2.** Main haplotypes related to genetic predisposition to develop diseases associated with EBV.

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| **Haplotipes** | **EBV-associated diseases** |
| DR2-DQ6 (DRB1\*1501, DQA1\*0102, DQB1\*0602). | It correlates positively with:   * Systemic lupus erythematosus (19–22). * Sjögren's syndrome (23,24). * Multiple Sclerosis (25,26). * Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (27,28). * Late-onset/acquired myasthenia gravis (29,30). * Fulminant type diabetes (31). * Hodking lymphoma (32,33).   It correlates negatively with:   * Type 1 diabetes mellitus (31,34). * Graves' disease (35). |
| DR3-DQ2 (DRB1\*0301, DQA1\*0501, DQB1\*0201). | It correlates positively with:   * Systemic lupus erythematosus (22). * Multiple sclerosis (36). * Diabetes mellitus type 1 (37,38). * Celiac disease (39–41). * Graves' disease (42,43). * Sjögren's Syndrome (23,24). * Early-onset myasthenia gravis (29,44,45). |
| DR4-DQ8 (DRB1\*04, DQA1\*03, DQB1\*0302). | It correlates positively with   * Multiple Sclerosis (36). * Diabetes mellitus type 1 (37,38). * Celiac disease (39–41). * Rheumatoid arthritis (46,47) * Hashimoto's thyroiditis (42,43). |

**Supplemental Table 3.** Current therapeutic strategies for ME/CFS.

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| **Medication** | **Examples** | **Effect** |
| Corticosteroids | -Hydrocortisone  -Frudocortisone | Some improvement in ME/CFS symptoms, especially physical fatigue (5), but suppression of adrenal gland hormone production, can lead to depression and weight gain. |
| Supplements | -Nutritional supplements  -Acetyl-l-carnitine, -Essential fatty acids  -Magnesium  -Vitamins  -Coenzyme Q10 plus | Improvement of physical and mental fatigue in ME/CFS patients with specific nutritional deficiencies. (6,7) |
| NSAIDs | -Ibuprofen  -Naproxen  -Celecoxib | Relief of joint, muscle, and headache pain, reduces fever and inflammation (8). Chronic use can lead to ulcers, bleeding, and gastrointestinal symptoms. If ME/CFS had a viral origin, selective COX-2 inhibitors, such as celecoxib, could be useful in the treatment of latent infections, since COX-2 plays an important role in viral replication and is positively regulated during viral infection (9). |
| Antiviral Drugs | -Rintatolimod  -Valacyclovir  -Valganciclovir | Rintatolimod is a TLR3 agonist that improves exercise tolerance and allows a reduction in the concomitant use of CFS/ME related drugs by improving NK cell function and influencing the 2-5A-synthetase pathway (10,11).  ME/CFS patients with elevated antibodies to Epstein-Barr Virus (EBV) have experienced significant improvements in physical activity when taking valacyclovir (12).  Statistically significant improvements in cognitive function and a reduction in mental fatigue have been observed in ME/CFS patients who also had elevated serum IgG titers for EBV and human herpesvirus 6 (HHV-6) (13). |
| Monoclonal Antibodies | -Rituximab | Improvement of symptoms by decreasing activity and number of B cells (14,15). However, a subsequent Norwegian trial found no significant difference from placebo (16), which may be due to the inclusion criteria used, which currently do not differentiate the ME/CFS subgroups according to cause. It could benefit only the ME/CFS subgroup post EBV infection. Deletion of normal B cells may also increase the risk of other infections. |
| Selective serotonin-reuptake inhibitors | -Fluoxetine  -Sertraline  -Paroxetine | Used in those patients with ME/CFS who have anxiety, depression and other mood disorders, as well as patients with chronic neuropathic pain (17). They can generate insomnia, agitation and gastrointestinal symptoms. |
| Tricyclic antidepressants | -Amitriptyline  -Doxepin  -Nortriptyline  -Desipramine | It has an anxiolytic effect, improves locomotor activity, sleep, and relieves pain in lower doses than those used to treat depression (7,18). They can cause drowsiness, sedation, weight gain, urinary retention, cognitive impairment, and sexual dysfunction. |

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