

PENE is Post Exertional Neuroimmune Exhaustion

(PENE) is a compulsory **neuroimmune** symptom in the **International Consensus Criteria** diagnostic criteria for **Myalgic Encephalomyelitis**.

This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the **neuroimmune** regions. Characteristics are:

- Marked, rapid physical and/or cognitive fatigability in response to **exertion**, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a **relapse**.
- Post-exertional symptom exacerbation: *e.g.* acute **flu-like symptoms, pain** and worsening of other symptoms.
- Post-exertional **exhaustion** may occur immediately after activity or be delayed by hours or days.
- Recovery period is prolonged, usually taking 24 hours or longer. A **relapse** can last days, weeks or longer.
- Low threshold of physical and mental fatigability (**lack of stamina**) results in a substantial reduction in pre-illness activity level.

From ICC 2011: Carruthers, BM; van de Sande, MI; De Meirleir, KL; Klimas, NG; Broderick, G; Mitchell, T; Staines, D; Powles, ACP; Speight, N; Vallings, R; Bateman, L; Bell, DS; Carlo-Stella, N; Chia, J; Darragh, A; Gerken, A; Jo, D; Lewis, DP; Light, AR; Light, KC; Marshall-Gradisnik, S; McLaren-Howard, J; Mena, I; Miwa, K; Murovska, M; Stevens, SR (2012), Myalgic encephalomyelitis: Adult & Paediatric: International Consensus Primer for Medical Practitioners (PDF), ISBN 978-0-9739335-3-6

Postexertional neuroimmune exhaustion is part of the body's global protection response and is associated with dysfunction in the regulatory balance within and between the nervous, immune and endocrine systems, and cellular metabolism and ion transport. The normal activity/rest cycle, which involves performing an activity, becoming fatigued and taking a rest whereby energy is restored, becomes dysfunctional.

Numerous papers document abnormal biological responses to exertion, such as loss of the invigorating effects of exercise, decreased pain threshold, decreased cerebral oxygen and blood volume/flow, decreased maximum heart rate, impaired oxygen delivery to muscles, elevated levels of nitric oxide metabolites and worsening of other symptoms. Patients reach the anaerobic threshold and maximal exercise at a much lower oxygen consumption level. Reported prolonged effects of exertion include elevated sensory signaling to the brain that is interpreted as pain and fatigue, elevated cytokine activity, delay in symptom activation and a recovery period of at least 48 hrs. When an exercise test was given on two consecutive days, some patients experienced up to a 50% drop in their ability to produce energy on the second evaluation. Both submaximal and self-paced physiologically limited exercise resulted in PENE.

As early as the 1950s, Dr. Melvin Ramsey, the infectious disease physician who created the term "myalgic encephalomyelitis" after seeing multiple patients with the same unusual presentation, considered "as the sheet anchor of diagnosis", "muscle fatigability, whereby, even after a minor degree of physical effort, three, four or five days, or longer, elapse before full muscle power is restored"

There are two small case-control studies from the Workwell Foundation. After being subjected to 2 cardiopulmonary exercise tests (CPET) separated by 24 hours, a total of 41 females completed an open-ended questionnaire about their symptoms for up to a week after the tests.

Thirty-seven healthy, sedentary subjects served as controls. The researchers examined their responses and coded them under symptom categories, as dictated by the CCC. The ME subjects experienced some symptoms the healthy subjects did not experience at all (e.g. lightheadedness, sore throat/ swollen glands, cognitive dysfunction) and were significantly more likely to experience other symptoms (e.g. pain (odds ratio (OR) = 15.7, $p < 0.01$) and sleep disturbance (OR = 37.5, $p < 0.001$)) compared to their healthy counterparts.

Using a binary logistic regression model, only 4 post-exertional symptoms (fatigue-, immune-, sleep-, and pain-associated symptoms) were needed to classify 92% of ME or CFS and 88% of healthy subjects accurately. The time course of symptoms also differed substantially: most control subjects experienced the peak of their symptoms on the day of the test and 87%-95% of them had recovered fully by 24 hours after the tests whereas some ME or CFS subjects' symptoms peaked 24 or 48 hours after the test with 45%-60% of ME/CFS subjects still feeling the effects after 5 days. Workwell found that if a subject was unable to recover fully within 24 hours, the positive likelihood ratio of them being classified as having ME or CFS was 11.4 whereas the negative likelihood ratio was 0.22. If a subject has this characteristic, it increases the clinician's baseline estimate of disease presence by about 45% whereas if they do not have this trait, their chances decrease by about 30%.

Historically, many promising initial results from ME and CFS studies have been contradicted or attenuated by subsequent studies. Consistent results from multiple, independent research groups in different settings can strengthen the validity of findings. Workwell's studies consisted of younger women (average age 31.5 ± 9.0 years) who were able and willing to complete 2 maximal exercise tests scheduled within 24 hours. Yet, about one-third of ME or CFS patients are estimated to be male and the illness is most common between the ages of 40 and 60. Furthermore, a significant portion of patients are unable to withstand even a single maximal exercise test and even relatively mild activity like dressing or driving have been reported to cause PEM in patient accounts.

Would a more representative group of patients engaging in less demanding tasks contend with a similar pattern of symptoms? Finally, while an open-ended questionnaire is indispensable when beginning to document a phenomenon, such a format may require more time and effort from patients to complete and clinicians and researcher to analyze when used in large studies or in a busy clinic. Open-ended answers may also be interpreted in a variable manner.

Consequently, the main purpose of the study is to describe the symptoms and time course of PENE in a systematic manner by surveying a large number of subjects afflicted by ME or CFS (PEM) with both close- and open-ended questions. We hypothesized our results would support prior descriptions of PENE and the Workwell Foundation's findings but provide additional details regarding specific symptoms and timing. We also asked subjects about their reactions to physical and cognitive effort versus emotional distress to determine if there are any differences in presentation of PENE when different stressors are applied.

<https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0197811>

The overwhelming majority of subjects diagnosed with PENE for ME or PEM for CFS experienced physical/ cognitive exertion and emotional upheaval. Aggravation of multiple symptoms, is the rule rather than the exception. Some symptoms are commonly observed with physical exertion even in healthy people (e.g. muscle pain) while others are atypical (e.g. flu-like feelings, gut-related symptoms, sensory overload), neither reported by healthy people nor people affected by other medical conditions. With ME or CFS there are specific symptoms rather than combinations (e.g. "sore throat/ tender lymph nodes") or categories of symptoms.

Patients readily discuss such factors when their illness experiences are validated. Subjects experienced the same array of diverse symptoms with emotional distress as provoked by exertion albeit at a lower rate. They also encountered symptoms such as musculoskeletal pain and sore throat that are usually not linked to emotional distress in healthy people or many people affected by other conditions.

ME patients report significantly greater symptom intensity elevation than do sham exposed patient and healthy control cohorts). Along with neuropathies and peri-neural adhesions, these issues represent potential ongoing sources of nociceptive input and glial activation, resulting in enhanced peripheral and central nervous sensitivity ([Rowe et al., 2013](#)). Peri-neural adhesions are fibrous bonds proximal to nerve tissues, often formed during post-operative/injury healing.

ME patients tend to have low cardiac output and the vast majority experience orthostatic intolerance, a manifestation of dysautonomia relating to inadequate blood circulation and attributable to hypovolemia/blood pooling in the extremities. Various regulatory neurotransmitter/(neuro)endocrine abnormalities, as well as (related) sympathetic nervous system (SNS) dominance and diminished cardiac mass may account for such features. Additionally, cerebral vascular control appears closely related to skeletal muscle pH, found to be elevated in ME at rest, and it has been hypothesized that compromised skeletal muscle cellular membrane function may lead to a degree of acidity equalization between the skeletal muscle intracellular environment (raised pH) and the blood (lowered pH). Consistent with these relations, abnormally prolonged cerebral vasoconstriction following orthostatic challenge is routinely observed in ME, this has ramifications for neural health, plus other deleterious effects including cerebral hypoxia and neurocognitive deficits.

Myalgic Encephalomyelitis is a highly intrusive disease which involves varying degrees of physical disability and cognitive deficits, associated psychosocial difficulties, and significantly reduced quality of life and life expectancy, across a patient population numbering in the millions worldwide. Complete/spontaneous recovery is extremely rare and conventional treatment strategies rarely deliver even modest direct, objective and, sustained symptomatic improvement. Thus, ME constitutes a particularly enigmatic, debilitating, and costly major public health issue, and the advancement of our understanding of its essence, hence, a pressing area of biomedical enquiry.

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