Nationales Referenzzentrum für postvirale Syndrome

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Miller CM, Moen JK, Iwasaki A. The lingering shadow of epidemics: post-acute sequelae across history. *Trends in Immunology*. 2026;47(1):9-18. https://doi.org/10.1016/j.it.2025.10.010

Post-acute infection syndromes – historical continuities and current challenges

Long COVID (more precise: post-COVID condition) has also brought other post-acute infection syndromes (PAIS) back into the spotlight of research and clinical practice. These syndromes can occur following infections with a wide variety of pathogens, including viruses, bacteria and parasites. In their article, Miller and colleagues highlight the historical roots of PAIS and emphasise the urgent need for integrated approaches to improve our understanding of their pathophysiology and develop effective therapies.

PAIS did not emerge with the onset of the COVID-19 pandemic. Despite their high disease burden, they have not been adequately researched to date. This decades-long research gap has resulted in a current lack of practical diagnostic biomarkers, making it difficult to recognise and differentiate some of these diseases and syndromes. Many patients also report stigmatisation and psychologization of their symptoms by the healthcare system – a pattern that has been observed repeatedly throughout history.

Following the Russian influenza pandemic of the 1890s, a condition called 'influenza exhaustion' was described, with clinical features resembling those of Long COVID today. After the 1918 influenza pandemic (H1N1), doctors observed a high prevalence of a post-acute syndrome that became known as *encephalitis lethargica*. Another example is post-polio syndrome, which occurred after the polio epidemic in the United States in 1952 and is now recognised as a distinct disease. PAIS have also been documented following outbreaks of SARS, Ebola, and Q fever. Additionally, endemic infections such as Epstein–Barr virus, Lyme disease and Chikungunya are known to trigger post-acute syndromes.

A key example of a PAIS is ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome), which was first described by A. M. Ramsay in 1955. There were repeated outbreaks in the 20th century, and in 1969, the World Health Organization classified ME as a neurological disease. Nevertheless, the disease was long psychologised and associated with hysteria, partly because women are more frequently affected. Although studies conducted after an outbreak in Lake Tahoe in the 1980s revealed structural brain changes, immunological abnormalities and increased reactivation of human herpesvirus 6, in 1988 the Centers for Disease Control and Prevention renamed the disease 'chronic fatigue syndrome' at the instigation of a small group of doctors, shifting the focus from an infectious origin to non-specific fatigue.

Today, possible disease mechanisms for ME/CFS include immunological, vascular and mitochondrial dysfunction, changes in the gut microbiome, and autonomic dysregulation. Diagnosis is made according to international clinical criteria, with post-exertional malaise (PEM) being the core feature. ME/CFS patients have a lower health-related quality of life than people with numerous other serious multisystem diseases, including lung cancer, multiple sclerosis and kidney failure.

These historical examples demonstrate that post-acute infection syndromes are not a medical novelty. However, they have recently received renewed attention in the context of Long COVID. The authors emphasise that PAIS can provide valuable insights into immunopathogenic mechanisms that are also relevant for Long COVID and ME/CFS. Given the increasing prevalence, there is an urgent need for better clinical and laboratory-based detection. Unanswered questions surrounding the pathomechanisms, treatment options and prevention of PAIS highlight the need for targeted investment in PAIS research to improve care and treatment in the long term.