

ABSTRACT: The incidence of Long COVID (LC) increases with age but then drops sharply in over 70-year-olds. The prevailing explanation is that different biases in data collection such as reluctance to report symptoms or attributing them to comorbidities may explain this pattern in this age group. Our local data suggested a similar pattern confirming the rarity of LC symptoms especially fatigue in the over 70s. Our data have also showed a different phenotype of post COVID fatigue which is not commonly associated with post exertional symptoms bringing into question the suggestion that bias in collecting data is the main cause. We explore several immunological, metabolic and epigenetic factors associated with aging that may explain such phenomenon.

KEYWORDS: Long COVID, elderly, post exertional malaise, post COVID syndrome

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Introduction

Post exertional malaise (PEM) is one of the hallmarks of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).¹ Several ME/CFS diagnostic criteria go as far as excluding the diagnosis of the condition in the absence of PEM.² As post COVID fatigue is believed to share the same origins and pathophysiological processes of ME/CFS, it is not surprising that PEM is one of the major features of post COVID syndrome or Long COVID (LC) as it is popularly known.^{3,4}

The similarities between ME/CFS and LC are naturally more extensive. Both conditions are more common in middle-aged females with ME/CFS being extremely rare to have its onset in the elderly patients.⁵ Despite having such severe acute COVID 19 infections,⁶ patients over 70-year-old risk of LC is dramatically reduced compared to their younger counterparts.⁷ Several explanations were suggested for this paradox of a population having on one hand a more severe acute illness but less prevalent long-term complications. The high mortality, low symptoms reporting in the elderly population and attribution of symptoms to other comorbidities were all suggested to explain this reduction of LC risk.⁸

More than 100 symptoms are traditionally attributed to LC which naturally leads to significant challenges comparing data from different studies or analysing large data sets in general. Post COVID fatigue mimicking ME/CFS is one of the most common phenotypes of LC and both conditions present with PEM in particular which is commonly associated with other post exertional symptoms such as pain, headaches, brain fog and recurrent sore throats.³ With the exception of respiratory symptoms, other LC symptoms such as thromboembolism, skin rash etc are exceedingly less common and seem to have a more organ specific pathogenesis.⁹

Methods

Long COVID service in Wigan (North England, population 326 000) was established in late 2020. The service has different arms mirroring the common LC phenotypes with a fatigue management team and respiratory team being the largest treating the bulk of the referrals.

Assessment of fatigue pattern for patients referred to that arm of the service included documenting demographic data and also the pattern of fatigue and if it is associated with PEM (as defined as worsening symptoms following physical or mental exertion lasting days or weeks) or if the fatigue is a standalone symptom with or without unrelated symptoms such as respiratory/cardiac/dermatological symptoms etc.

Results

We have reviewed the data of 532 referrals that we received from November 2020 to November 2022.

Only 17 (3.1%) over 70 patients were referred to our fatigue management service. Thirteen were females. The age range was 70 to 79 years. The duration from onset to referral was 4 to 24 months (mean 10 months). No referrals were received for over 80 year old patients.

Only 7 out of 17 of the over 70 referrals had their fatigue associated with post exertional malaise. One of these 7 patients had a history of fibromyalgia and her PEM preceded COVID-19 infections. Only 6 patients had a significant comorbidity.

A total of 482 out of the 515 under 70 patients had PEM associated with their fatigue (93.5%).

Discussion

Our data not only confirms the rarity of post COVID fatigue in subjects over 70 but also suggest that when fatigue occurs in



Table 1. Factors that may explain the low incidence of post COVID fatigue in the over 70s.

FATIGUE ASSOCIATED WITH PEM	COMMON IN YOUNGER POPULATION	RARE IN OLDER POPULATION
Bias in data collection	Low mortality following acute COVID-19 infection	High mortality following acute COVID-19 infection
	Symptoms attributed to LC as comorbidities are rare	Symptoms might be attributed to common comorbidities
	More common to seek medical advice	Less common to seek medical advice
Psychosocial factors	Active lifestyle with stressful life events (care responsibilities, relationships and financial)	Less active lifestyle less likely to have stressful life events
Metabolic	Hypermetabolic response	Hypometabolic state
Immunological	Deregulated	Less robust immune response
Epigenetic	Changes common with stress	Changes common with aging

that age group, it is not strongly associated with PEM or other post exertional symptoms.

The phenomenon of PEM is poorly understood; however, the available literature suggests several immunological, metabolic and epigenetic factors to play different roles in its pathogenesis.^{10,11} At the moment, the available evidence is not sufficient to establish a clear sequence of events or causality, however, the initial trigger seems to stem from a failure of the aerobic pathway to respond adequately to the increased energy requirements after exercise or stress.¹² Subsequently, a hypermetabolic process, immunological deregulation and epigenetic changes take place.^{10,13} These changes do not just fail to compensate for the inadequate aerobic metabolic responses but also induce the classic symptoms of PEM.

The metabolic effects of aging are equally complex but hypometabolism is a constant feature.¹⁴ We can hypothesise that such limited metabolic response to exercise and/or stress may protect the patient from the typical hypermetabolic phenomena and its subsequent symptoms of PEM.

The nature of immune response in ME/CFS is unknown with the limited studies available reporting inconsistent findings.¹⁵⁻¹⁷ This inconsistency may explain the wide variety of immunological symptoms ME/CFS patients experience ranging from impaired immunity leading to recurrent infections to an exaggerated immune response resulting in the classic symptoms of malaise, recurrent sore throats, lymphadenopathy and occasionally full blown autoimmune phenomena such as allergies.

In general, aging is associated with weaker immune responses¹⁸ which are associated with complex epigenetic, inflammatory and physiological changes that naturally induce significantly different responses to exercise and stress when compared to the younger population. Deconditioning and frailty can also play a role in this population presenting with fatigue with no associated PEM.

At the moment, the prevailing hypotheses explaining the rarity of Long COVID in the elderly population are bias in data collection and/or biopsychosocial factors (Table 1). Our

data is small, and observational. Because of its retrospective nature, there were several gaps hence, the limited data analysed as being the ones we can confidently ensure its accuracy. Having said that, If our findings could be replicated in a larger population, we feel that exploring the physiological changes associated with aging may not only explain such unique post COVID fatigue phenotype in the elderly (fatigue without PEM) but may also shed some light on the illusive ME/CFS and Long COVID pathogenesis.

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