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Post Covid Syndrome and Cognitive Dysfunction – Aetiology and Possible Treatment

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Abstract

Background: Cognitive dysfunction is not infrequent after recovery from SARS-Cov-2 infection and often accompanied by fatigue and several of the other symptoms seen in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Post-Covid Syndrome (PCS) inflammation impairs mental function through a combination of altered attention and cognition. Here we discuss the relationship between infection, peripheral and central inflammation, and cerebral and cognitive dysfunction in patients with PCS.

Methods: Review of the relevant literature and personal clinical research work.

Results: Cognitive dysfunction in PCS is multifactorial and has several similarities to that in ME/CFS. It likely arises from low grade persistent inflammation associated with sleep dysfunction and altered mood with endothelial dysfunction leading to altered regional cerebral blood flow and accompanied by disturbed neuronal function. Immune dysregulation initiated by reactivation of previously acquired herpes type viruses and leading to reduced mitochondrial energy generation and subtle autoimmunity targeting one or more neuronal and autonomic receptors may also be contributing factors. Treatments used in ME/CFS, and aimed at these factors, used collectively may provide benefit.

Conclusion: Reducing low grade systemic inflammation, viral reactivation and immune dysregulation has the potential to improve cognitive dysfunction in PCS.

Keywords: SARS-Cov-2, Cognitive dysfunction, Neuro-inflammation, Endotheliopathy, Cytokines, Immune dysfunction, Viral reactivation, Cerebral blood flow, Treatment

Introduction

It is now generally accepted that 'Long-COVID' or post-covid-19 syndrome (PCS) comprises a number of variably disabling symptoms persisting 12 weeks after a confirmed Covid-19 infection [1]. According to recent global analyses, the cumulative prevalence of PCS varies widely from between 9% to 63% [2]. Regardless, it is suggested that it is up to 6-fold more able to cause long term disability than similar post-viral infection conditions [3]. In respect to the symptoms seen in Long-Covid, these include many that are also seen in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) [4-6] raising the possibility that PCS is a subset of this condition induced by a known viral trigger. Most frequent amongst these symptoms in long-Covid are chronic fatigue, subjective shortness of

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breath, cognitive impairment / brain fog, delayed post-exertional malaise, impaired short term memory, unrefreshing sleep, palpitations, musculoskeletal pain and headaches [1, 7]. However, PCS also has some symptoms that appear more unique and include spasms, cough, altered smell / taste, chest pain, and depression. Several factors, including many relating to the severity of the infection, appear to predispose to PCS. These include female sex, older age, cigarette smoking, pre-existing medical conditions, lack of COVID-19 vaccination [8], infection with pre-Omicron SARS-CoV-2 variants [9], number of acute phase symptoms, viral load, severe / critical COVID-19 illness, as well as invasive mechanical ventilation [2]. The precise cause of PCS remains unclear and multiple, often overlapping causes have been proposed [10]. Notwithstanding, treatment of the CD in both PCS and ME/CFS is difficult but with a better understanding of the mechanisms involved in CD, therapy tailored to the prevailing patho-mechanisms operative in an individual may be offered [11]. However, much can be gained from the experience of managing fatigue and CD in ME/CFS that can benefit those with PCS.

Frequency of Cognitive Dysfunction in PCS

Cognitive dysfunction (CD), memory loss and attention disorder have been reported to be especially frequent in those with PCS [12, 13] and affect between one third and one quarter of all such individuals [13-15]. Mechanistically, fatigue and CD appear to share several common underlying predictors [16]. These include raised levels of apathy, anxiety, and executive dysfunction in neuropsychiatric measures and executive and attentional difficulties on cognitive tests. While, it is likely to be partly caused a combination of fatigue and neuropsychiatric symptoms including depression and anxiety, several medical and immune issues are also critical.

Mechanism of CD in PCS

The cause of the CD in long-Covid is unclear and likely multifactorial as it is in ME/CFS and likely involves a combination of one or more mechanisms [17]. Figure 1 summarises the main factors which may contribute to CD in PCS. Given the serious nature of the acute illness and the requirement for prolonged convalescence in some, it is unsurprising that depression and anxiety are important in these patients [18, 19] and frequently complicated by disturbed sleep [19]. The latter is critical to normal immune function and sleep disturbance can certainly contribute to and be affected by peripheral and central inflammation [20] which is not infrequent even 3 months after recovery from acute SARS-Cov-2 infection [21]. Interestingly, urine metabolomics analysis in both PCS and ME/CFS has shown significant changes in the downstream metabolites of tryptophan and tyrosine including serotonin, dopamine and catecholamines [22]. As such as evidence for low mood and continued anxiety is frequently sought and appropriate treatment offered. In this respect, efforts should also be made to determine the presence of an underlying joint

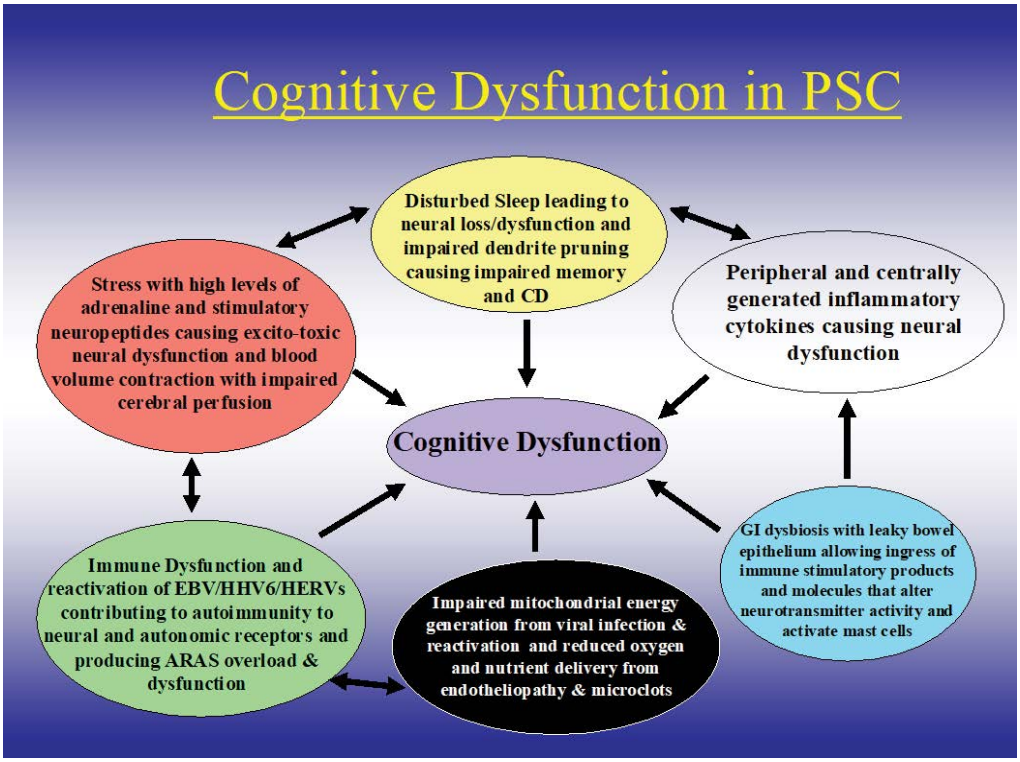

Figure 1: Important factors contributing to cognitive dysfunction in PSC.

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hypermobility syndrome (JHS). This is over represented in both PCS and ME/CFS and frequently associated with marked anxiety and cognitive dysfunction [23, 24] and complicated by orthostatic intolerance and sometimes postural orthostatic tachycardia (POTS) [23, 24]. Unchecked, the combination of chronic anxiety and JHS/POTS is especially disabling as central blood volume contraction caused by dysregulated catecholamine secretion [25, 26] and impaired cortisol secretion from pituitary dysfunction [27] can perpetuate and aggravate ill health and CD. Furthermore, impaired cortisol secretion can also adversely affect sleep and hence cognition and memory consolidation [28]. Certainly, cortisol is important in modulation of several neurotransmitters and neuropeptides that are important in cognitive appraisal and regulatory physiology [29]. Conversely raised cortisol, as occurs in any acute illness, can if prolonged post recovery, as result of ongoing stress and anxiety, produce structural changes in the hippocampus and prefrontal cortex with impaired memory and CD [30].

In PCS patients who have previously required intensive care treatment, evidence of cardiorespiratory dysfunction leading to hypoxia and/or impaired cerebral blood flow should be diligently investigated and the possibility of post-ITU syndrome borne in mind. However, in-depth exercise testing suggests that the reduced exercise intolerance, dyspnoea and fatigue are often not the result of deconditioning and the haemodynamic and gaseous exchange abnormalities are similar to those seen in ME/CFS [31]. Corroboration that PCS is not the result of deconditioning has also been provided more recently by Leitner et al [32]. They reported metabolomic evidence of impaired aerobic and anaerobic respiration in PCS patients undergoing invasive cardiopulmonary testing and associated with impaired energy generation. However, given the importance of muscle tissue as a source of brain derived neurotrophic factor, that is important in neural integrity and function, it is critical that regular movement is maintained [33, 34]. In this regard, a hypometabolic state has been reported in patients with ME/CFS with abnormalities in 20 metabolic pathways and a phenotype similar to dormancy in animals [35]. Impaired mitochondrial ATP generation and particularly with increased demand has been considered evident in ME/CFS for several years [36, 37] and now more recently in PCS [38]. Given that the brain requires significant amount of energy, it is therefore not surprising that any constraints on ATP generation by mitochondria will negatively impact on cognitive function.

In terms of the immune system, dysfunction with activated innate immune cells, diminished naïve T and B cells and raised type 1 and type 3 interferons, is not infrequent in those with long-Covid [39]. As such viral persistence and possible central neuroinvasion with disturbed immunological responses and autoimmunity may well be important in many as well as the ability of type 1 interferons to alter neuronal signaling [40]. Moreover, microvascular clot formation from SARS-Cov-2 protease activity and complement activation, and endotheliopathy [41] may contribute to inadequate neural oxygenation and nourishment. There is also evidence of oxidative overload and activation of TGF-β signaling as well as neuropathological pathways causing tau hyperphosphorylation that are typically associated with Alzeimhers disease [42] in those with long-Covid. Although Mazza et al [21] observed raised parameters of inflammation 3 months after discharge from hospital in patients with SARS-Cov-2 infection, the levels of several inflammatory cytokines during the acute and long phase of SARS-Cov-2 infection could not be associated with the CD in those with long-Covid [43].

It is also possible that the immune dysfunction following SARS-Cov-2 infection permits reactivation of EBV [44], HHV-6 and human endogenous retroviruses viruses that are collectively responsible either directly or via autoimmune mechanisms for the CD [45, 46]. Indeed, raised antibody titres against EBV are evident in PCS [47]. Additionally, endothelial dysfunction with disrupted blood brain barrier integrity evident on dynamic contrast enhanced MRI and associated with compromised nutrient delivery to central nervous system cells may well be important [48]. Interestingly, peripherally generated SARS-Cov-2 spike protein has been shown to produce neuroinflammation and hippocampal gliosis which could be inhibited by Toll-like Receptor (TLR) 4 blockade [49]. Notwithstanding, several factors may interact and thus endothelial dysfunction may be permissive of microclot formation [50] and especially fibrinaloid microclots containing several inflammatory proteins as well as those from activated platelets [51].

Pathologically, SARS-Cov-2 infection in humans and in mice has been associated with white matter microglial cell activation, impaired hippocampal neurogenesis, myelin loss and reduced oligodendrocyte numbers [52]. Changes in endothelial function affecting cerebral perfusion and arising from diminished plasmalogens in cell membrane phospholipids may also be important in PCS and ME/CFS [53]. However, while direct neural invasion is considered extremely rare, actual SARS-Cov-2 RNA within neural cells expressing the ACE-2 viral receptor [54] and neuropathological changes have been described and with inflammation demonstrated most frequently in the brain stem [17]. Interestingly, similar patterns of abnormal brain stem volumes have been reported in both ME/CFS and PCS [55]. CD may therefore arise from a dysfunctional filtering mechanism of external stimuli within the ascending reticular activating system in the brain stem [56].

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Dysbiosis within the respiratory tract in PCS is not infrequent in PCS given adverse effect of SARS-Cov-2 on immune function, compromised airway function and use of antibiotics and other immune modulating agents in the acute infection [57, 58]. However, gastrointestinal (GI) symptoms including especially nausea and diarrhoea have been described in up to a fifth of people with SARS-Cov-2 infection and the virus has been isolated from stools and anal swabs in half [59]. Importantly, faecal *Firmicutes*, *Bacteroidetes* and *Proteobacteria* have been found to be raised in adults and children with SARS-Cov-2 infection [60]. However, ~~but~~ six months after acute infection, patients without PCS had recovered GI microbiomes while those with PCS manifested higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus* and lower levels of *Faecalibacterium prausnitzii* [61]. Interestingly, 'persistent respiratory symptoms correlated with opportunistic gut pathogens, and neuropsychiatric symptoms and fatigue correlated with nosocomial gut pathogens, including *Clostridium innocuum* and *Actinomyces naeslundii* [61]. Moreover, butyrate-producing bacteria, including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii,* exhibited the greatest inverse correlations with PCS at 6 months. Thus, GI dysbiosis with altered tryptophan and glutamate metabolism, reduced short chain fatty acid production [62] and changes in tolerogenic bacteria that positively modulate inflammation and immune responsiveness may contribute to several of the neurological problems seen in PCS [57, 60]. Indeed, microbiota that encourage inflammation and leakage of the bowel epithelium may alter the synthesis and increase the absorption of several amino/keto acids and serotonin that impact significantly on attention, cognition and mood as they have varying abilities to stimulate specific neural receptors [62, 63]. More recently the role of mast cells has been explored as many patients with PCS manifest symptoms suggestive of mast cell activation [64] and mast cells have been described peri-vascularly close to neurones within the CNS [65]. Importantly, MCs are capable of releasing a variety of inflammatory cytokines and chemokines [66] in response to stress [67] and with viral infections [68].

Immune dysfunction and viral reactivation in PCS and ME/CFS

Evidence suggests that rare genetic variants predictive of loss-of-function of Toll-like receptor 3 and 'interferon regulatory factor 7 (IRF7)-dependent type I interferon (IFN) immunity to influenza virus' are more frequent in those with severe life threatening SARS-Cov-2 infection [69]. In contrast it is unclear whether prior primary or secondary immune deficiency appears to predispose to severe SARS-Cov-2 over and above the effect of established adverse parameters such as age, on-going lung disease etc [70]. As such patients with ME/CFS and those with PCS without lung damage do not suffer recurrent upper respiratory tract deficiency in the same was as patients with primary antibody deficiency (PAD). However, it is interesting that the frequency of ME/CFS type symptoms is markedly raised in patients with PAD [71]. Previous studies have shown essentially normal immune parameters in ME/CFS [72] with some more recent ones showing low levels of IgG3 and IgG4 in 25% and reduced mannose binding lectin in 15% in a German cohort of patients [73]. In Austria, IgG subclass deficiency was evident in 17% and heterozygous reduced MBL levels in 32% and MBL deficiency in 7% [74]. Other immune variables reported to be decreased in patients with ME/CFS include NK numbers and function [75], reduced NK and T cell perforin [76] and function [77]. However, as with PCS, it is again notable that there is no evidence for clinically overt viral reactivation in the form of recurrent severe shingles, herpes labialis, warts etc. Interestingly, elevated salivary antibody levels to EBV, HHV-6 and HERV-K were detectable in ME/CFS patients 3 to 6 months after mild SARS-Cov-2 infection [78]. Additionally, reactivation of HHV6 has been considered important in the development of autoimmunity to tight junction proteins and neural proteins in those with PCS [79]. Prior to this in 2019, Rodrigues et al [80] investigating patients with ME/CFS found evidence of HERV-K but thankfully not HERV-W reactivation which may contribute to enhanced autoimmune damage to the myelin sheath and extending to the axons in a mouse model of multiple sclerosis [81]. Prior to this Oakes et al [82]using different techniques found no evidence of HERV-K18, HHV6 or HHV-7 activation. Regardless, a subtle impairment of cellular immunity in ME/CFS and in PCS may be present and without obvious clinical immune suppression. This may allow previously acquired viruses to escape control and thus therapies causing immune suppression need to be utilised with care and especially those that might reduce T cell regulation of herpes virus control.

Long term recovery and CD in PCS

Recovery from PCS appears to vary in different studies and after one year was just under 70% in adults and 93% in children in a Japanese study [83]. In France these figures were lower and with an improvement in most symptoms but an increase in some such as fatigue and paraesthesia after 6 months [84]. In Switzerland, 23% of confirmed Covid-19 patients had not recovered by 6 months, 18.5% by 12 months and 17.2% by 24 months [85]. In many individuals not recovering from their SARS-Cov-2 infection with persistent physical and mental fatigue are significantly disabling [86] and compounded by CD which has often be reported as 'brain fog'. However, both physical fatigue and CD showed an approximately 50% improvement over a one to two year period and thus substantial numbers remained unwell. The factors predicting poor improvement included significant depression and headaches at baseline as well as male sex,

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older age and fewer than 12 years of school education [86]. Interestingly, these researchers found SARS-CoV-2 reinfection to have no significant impact on recovery from fatigue or cognitive deficits. Separately, Legler et al [7] noted recovery to be lower in those PCS patients who also fulfilled the criteria for ME/CFS [7].

Treatment of CD in PCS – what can be learned from ME/CFS

Respiratory exercises and especially several varieties of controlled breathing as well as deep relaxation and muscle strengthening exercises have been advocated for people with PCS and those with ME/CFS with some but not definitive evidence [87]. Where marked anxiety and depression complicate the recovery, suitable medications are also utilised. Resilience training, support and understanding in the early part of recovery may also be helpful in improving coping ability and reducing CD in the long term [88]. As in ME/CFS, patients with PCS frequently contend that any lowered mood and anxiety are the result of the condition and not the cause. Too a fair degree this is also borne out by recent work suggesting neuroinflammation and a raised ~~a~~ 'neurotoxicity index' explain a significant part of the fatigue, depression and anxiety seen in PCS [89]. Low grade immune activation [90] and inflammation and especially within the central nervous system, as indicated by magnetic resonance imaging, magnetic resonance spectroscopy, electroencephalography and positron emission tomography [91] is evident in both ME/CFS and PCS. Consequently, several anti-inflammatory agents have been proposed for treatment although unfortunately there are few double blind randomised ~~placebo~~ controlled trials (DBRCT) for nearly all the agents in both of these conditions. However, efforts to reduce neuroinflammation by using flavonoids such as luteolin and quercetin has been proposed and based around their ability to reduce mast cell activation [64]. Other agents used open label in PCS and ME/CFS to reduce neuroinflammation include palmitoylethanolamide which has been suggested to work by multiple mechanisms including antagonism of the nuclear factor-κB (NF-κB) signalling pathway, anti-viral properties and reducing endocannabinoid metabolism [92]. Tocotrienol, a vitamin E analogue with marked anti-oxidant properties has been suggested for post covid lung fibrosis [93] but has also been found helpful for brain fog in those with PCS and ME/CFS by one of the authors. Similarly, natural dietary polyphenols such as Curcumin, Resveratrol, and Gossypol have been shown to have anti-bacterial/anti-viral properties and especially against SARS-Cov-2 [94]. Thus, they offer a significant potential to manage both acute and long-Covid and possibly also in those with post-viral ME/CFS. Indeed, curcumin combined with tocotrienol has been helpful in over half of the ME/CFS patients managed by one of the authors. Interestingly, some ME/CFS patients have found cannabis to improve their sleep and CD and suggestions for its use in PCS have recently been made owing to its ability to modulate neuroinflammation [95].

Overall, improvement in nutrition ~~and~~ with the use of vitamins C and D, to attenuate neutrophil dysfunction and excessive inflammation [96] and zinc, selenium, polyphenols, pre- and probiotics to optimise the gut microbiome have been suggested to improve anti-viral pathways and increase the delivery of factors that reduce depression and anxiety in SARS-Cov-2 and other viral infections [97]. Interestingly, combining vitamin D3, vitamin B6 and Zinc with 1gm of beta-glucan showed benefit for cognitive fatigue in over 36 weeks in 65 ME/CFS patients in a DBRCT [98]. In respect to supplements that improve CD by enhancing or optimising mitochondrial energy production such as Coenzyme Q10 [38] (Mantle et al, 2024), D-ribose, NADH and various forms of carnitine, the evidence is limited and based mainly on open label studies [99]. However, benefits for fatigue and mental clarity have been evident although frequently of short duration (personal observation Bansal). However, low dose naltrexone was found helpful in an open label study in ME/CFS [100] and a study investigating its use in long-Covid is planned [101]. While the precise mechanism of action of LDN in ME/CFS is unclear, restoration of NK cell Transient Receptor Potential Melastatin 3 (TRPM3) function has been suggested [102]. Recent work has shown vitamin B12 to have a significant SARS-Cov-2 anti-viral activity [103] and vitamin B12 can also improve overall anti-viral immune responses [104]. Interestingly, low serum Vitamin B12 levels have been shown to predict chronic fatigue six months after acute EBV infection [105] and intranasal vitamin B12 has been found to improve physical functioning in those with ME/CFS [106]. Furthermore, Regland et al [107] reported a positive dose response relationship in people with ME/CFS who injected vitamin B12 alongside oral folic acid. In PCS low levels of serum vitamin B12 at sixty days follow-up from the acute infection had prolonged poor physical functioning [108]. Our own experience in vitamin B12 injection therapy in over two thousand patients with ME/CFS and with doses varying between 1mg weekly to 1mg every 4 weeks has shown marked benefit for both physical fatigue and CD. Side effects were extremely rare and included reactivation of acne in a small proportion of mainly younger patients.

Much has been written about the immune system in ME/CFS [77] with impaired NK cell [109, 110], B cell [111] and T cell [45,75] function being most commonly reported . Unsurprisingly, there is evidence of reactivation of several herpes viruses such as EBV and HHV6 [112-115]. In consequence nucleoside analogues with variable activity against the common herpes viruses have been frequently used and benefits in physical and mental fatigue described [116, 117]. So far neuroimaging to show reduced CNS inflammation

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has not been undertaken although this is clearly a possible mechanism for improved CD. In the context of PCS, there is now significant evidence that the frequency of chronic fatigue and CD after SARS-Cov-2 infection is significantly lower after appropriate vaccination [14, 118]. Given that no precise viruses have been identified for those with ME/CFS, vaccination strategies are impossible although efforts against EBV continue primarily to reduce the development of various lymphomas and nasopharyngeal cancer. In regard to autoimmunity towards autonomic receptors and especially adrenoreceptor β2 and muscarinic M3, possibly initiated by EBV and related viruses [119-121], at least 2 reports have shown benefit from immunoadsorption [120, 122]. It is proposed that the removal of these auto-antibodies improves cerebral blood flow and certainly there is some correlation between auto-antibody levels and clinical symptoms [120, 122]. In those with IgG or IgG subclass deficiency, subcutaneous IgG replacement therapy was considered helpful in 5 out of 12 patients [123]. A critique of previous often short trials of intravenous immunoglobulin therapy in ME/CFS has shown shortcomings which if appropriately addressed may suggest its use in the future [124].

The observation that the S1 protein of SARS-Cov-2 may persist within monocytes and contribute to their activation has led to the trial of maraviroc, as an anti-CCR5 antagonist, with pravastatin as a fractalkine inhibitor [125]. Improvement in several validated clinical scales attributed to diminished adverse monocyte/endothelial cell interaction was found amongst the 18 participants in an open label study [125]. In contrast the initial hype of PSC being the result of fibrinaloid microclots [126] has diminished as long term anti-coagulation has not provided any significant benefit [127]. Hyperbaric oxygen therapy (HBOT) has traditionally been used in carbon monoxide poisoning, decompression sickness, smoke inhalation and radiation induced injury. However, it has now been utilised in strokes, traumatic brain injury and in neurodegenerative disorders and with favourable results [128]. Importantly, HBOT has multiple modes of action other than simply improving the delivery of dissolved oxygen. These include changes in various neuro-receptors, parasympathetic stimulation and stimulation of nitrous oxide [129]. While considered helpful in acute SARS-Cov-2 infection with hypoxia, in PCS, there is little data of HBOT from large controlled trials. However, from three small RCTs and case series there appears to be a mildly positive benefit [130]. In fibromyalgia, which is highly associated with ME/CFS, there is also evidence of benefit for both pain and CD [131, 132] and with rectification of abnormal brain imaging on SPECT analysis [131].

Conclusion

PCS is similar to ME/CFS in many ways and the CD in. both is under-recognised, frequent and ill understood. It is likely that the CD is caused by dysfunction of several bodily systems leading to reactivation of previously acquired viruses, subtle autoimmunity, impaired energy generation and disturbance of sleep, endocrine and GI function. While viral persistence as a causative factor is rare, there is significant evidence for low grade inflammation affecting CNS endothelial and neural cells and impairing nutrient delivery and function. PCS is more frequent in those with underlying JHS and recognition and treatment for ongoing stress related anxiety and depression is important as is therapy for any lingering cardio-respiratory compromise. Several of the treatments found effective in ME/CFS may be useful for those with PCS but high grade evidence supporting their use is scarce.

Conflict of Interest

Neither of the authors have any conflict of interest.

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