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Long-COVID: A New Name for a Long-Known Symptom Constellation

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Abstract

There has been intense interest in the past 18-24 months on the evolution of a symptom complex in individuals previously infected and/or vaccinated with SARS-CoV-2, which has been described to represent a novel entity, named long-COVID. Included in the symptoms are chronic fatigue, myalgias, depression/anhedonia, poor sleep and in some cases evidence for autoimmune-like responses. The potential drain on medical resources for effective treatment of this condition is enormous, and there is some urgency in developing an improved understanding of the pathophysiology behind it. In the review below we argue that this is unlikely in fact to represent a new entity, but a well-described entity of long-standing (myalgic encephalomyelitis/chronic fatigue syndrome, and fibromyalgia). Even simply pooling the limited data on our understanding of the etiology and treatment of these disorders is likely to improve substantially our ability to deal with the number of individuals presenting with long-COVID, and thus lessen some of the adverse psychological effects associated with “labeling” of this condition.

Keywords: SARS-CoV-2; Long-COVID; Fibromylagia; Vaccination

Abbreviations

ME: Myalgic Encephalomyelitis;CFS : Chronic Fatigue Syndrome

Introduction

Over the last 3 years the global community has been gripped by acute medical issues attributed to infection by COVID19 [SARS-CoV-2] [1]. This respiratory virus, like many identified before it, causes particular morbidity and mortality in the elderly (and the very young), and in those with identified prior respiratory ailments and other chronic comorbitities [2]. Infection of cells through binding of viral spike protein to a surface receptor on target cells results in a plethora of acute symptoms of SARS-CoV-2, especially in the lungs and respiratory tissue [3]. However, as time passes from focus on the acute symptomatology, evidence has accrued to indicate that many patients subsequently develop a chronic condition characterized by fatigue and neuropsychiatric symptoms, termed long-COVID [4]. However, as will be discussed in more detail below, a more critical analysis of the literature suggests that long-COVID is not in fact a novel disease, but representative of a condition known for some time and often referred to as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [ME/CFS, [5]]. This disorder was recognized often to begin in previously healthy individuals after an infection, of which the most common seemed to be infectious mononucleosis caused by EBV [5]. It is more frequent in women and there seems to be a genetic predisposition/susceptibility to the disorder. Symptoms of both ME/CFS and long-COVID include Post-Exertional Malaise (PEM), fatigue, orthostatic intolerance, cognitive disturbances, and sleep problems with inadequate restitution after rest, sensory hypersensitivity with pain, and symptoms related to autonomic and immune dysfunction. There is significant overlap of symptoms with those of a similar ailment referred to independently as fibromyalgia [6]. This is regarded as a musculoskeletal syndrome affecting between 1%-5% of the global population, again predominantly women, who in turn report pain, poor sleep, fatigue, depression, stress, and anxiety [7]. The review that follows considers the similarity of symptoms in long-COVID, ME/CFS and Fibromylgia to be manifestations of a common pathogenesis, associated with chronic inflammation, immune dysfunction and altered vascular flow in local tissue beds, which in turn trigger a number of compensatory adaptations aimed at restoring homeostasis which may cause further symptomatology.

Literature Review

Pathogenesis of ME/CFS

The major in this recent review has discussed a sequence of events which are proposed to contribute, in part at least, to the development of ME/CFS, a disease which often starts in previously healthy individuals after an infection (commonly infectious mononucleosis (EBV), and is more frequent in women with strong evidence for a genetic predisposition [5]. The prevalence rate quoted varies from 0.2%-0.8% of the population. An initial trigger is thought to occur with development of autoantibodies following an infectious insult, consistent with evidence for a role of augmented B cell stimulation/differentiation in ME/CFS, and the beneficial clinical effect of B

cell/IgG removal [8-13]. Fluge, et al. also postulate that autoantibodies to G-Protein-Coupled Receptors (GPCRs) cause a subsequent impaired autoregulation of tissue blood flow associated with an autoimmune-mediated perturbed endothelial activity (different from the mechanisms of impaired endothelial responses seen in cardiovascular disease) and an increased relative risk of tissue hypoxia [14-22]. This latter has been demonstrated in some ME/CFS patients who showed evidence of microcirculatory disturbances with impaired peripheral oxygen extraction, Arterio Venous (AV) shunting and a risk of neurovascular dysregulation and small fiber neuropathy [18]. It has been reported by many patients that transient symptom improvement occurs with oxygen inhalation, nitroglycerin-mediated vasodilation (which may even alleviate reported "brain fog"), and even from saline infusions to increase volume and venous pressure. Many of the CNS effects seen in ME/CFS, attributable to neuronal inflammation and associated with lactate accumulation and microglia activation may reflect impaired autoregulation of blood flow and brain tissue hypoxia caused by exertion (physical/mental) [19]. Autonomic dysfunction reported in ME/CFS, with increased sympathetic tone and altered sympathovagal balance likely reflect secondary and compensatory adaptations to inefficient blood flow regulation on exertion, and a number of compensatory metabolic changes may also be seen in attempts to maintain and restore energy supply caused by an underlying tissue hypoxia on exertion [20-22]. Interestingly, given the discussion below, Fluge, et al., concluded: "There is growing concern for patients that "long COVID…. the symptoms (of) which may resemble those of ME/CFS may be caused by subtle organ damage from the viral infection, or that subgroups of "long haulers" may have a post infectious immune disturbance and pathophysiology similar to those in ME/CFS [5].

It is important to note that both in patients with ME/CFS and fibromyalgia pain and sleep deprivation exhibit a bidirectional relationship, which itself interacts with depressive symptoms [23-25]. There is a lengthy literature on bidirectional interactions between sleep and immune function, and depression and immunity, particularly with respect to inflammatory cytokine biology, rather than the aforementioned induction of autoantibodies [6,8,9,14,26,27]. Thus there are known circadian rhythms associated with serum and CSF IL-1 and IL-6 production; chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor (TNFa) secretion from night time to day time; Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP, with even one night of sleep loss markedly impacting TNF levels in healthy men and sleep deprived mice have been reported to show altered cytokine production manifest by perturbations in serum IL-1ra, TNF , and IL-6 levels [28-33]. A review of the role of inflammatory cytokines in depression in humans can be found in Felger [27,29]. Given that most infectious disease episodes are associated with production of inflammatory cytokines through various perturbations in innate and/or acquired immunity, it should not therefore be surprising that following such infections disruptions in sleep and mood/behaviour are common, and a "cytokine storm" has itself been linked to morbidity/mortality following SARS-CoV-2 infection [34,35].

Overlap between ME/CFS and long-COVID

We have discussed at length elsewhere the lack of consensus related to the important biologic and immune parameters which are instrumental in effective host resistance following acute exposure to SARS-CoV-2 infection, stressing the lack of attention to induction of innate immune responses and mucosal immunity in the upper respiratory tract, the likely site of viral entry [36]. What detailed analysis is available supports the contention that the disease entity caused by this virus, and host response to it, is markedly similar to that of other known respiratory viruses of the Cornaviridae family [37]. Even less critical scientific thought has gone into understanding the outcome of chronic viral exposure, and the immunological and clinical outcomes of this, though, as noted above, there is already a growing literature on what has been referred to as "long-COVID", suggesting that this may represent a novel disease entity [4,38]. In a recent detailed demographic study of linked Electronic Health Records (EHRs) data from 81 million patients which included ~275,000 SARS-CoV-2 survivors, studied before implementation of any mass vaccination strategy (see: "Cohorts included all patients over the age of 10 who had the index event (COVID- 19 or influenza) on or after January 20, 2020 (the date of the first recorded COVID-19 case in the USA) and who were still alive at the end of follow-up (December 16, 2020") (39, over 50% of patients reported some symptoms of breathlessness, fatigue/malaise, chest/throat pain, headache, abdominal symptoms, myalgia, cognitive symptoms, and anxiety/depression in the 6 months following acute infection, and many reported persistence at 6 months. There were significant differences in incidence and co-occurrence associated with sex, age, and illness severity, suggestive of a susceptibility phenotype, though the hazard ratio in relation to these symptoms following SARS-CoV-2 compared with influenza was only increased to between 1.44-2.04. As with ME/CFS (above) sleep-related symptoms have also been reported common in subjects post SARS-CoV-2, and seem to be most manifest in those with the most severe acute disease, mostly ≥ 58 yr of age [39,40]. Similar findings to those of Taquet, et al., were made by Lopez-Leon, et al., who reported on ~48,000 patients (ages 17-87), finding that the most common persisting symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%); and Sandler, et al., who concluded that fatigue in particular was a prevalent outcome from many acute systemic infections (particularly EBV as note above), with a case rate for clinically significant post-infective fatigue up to 10%-35% at 6 months post infection [41]. Importantly Dennis, et al., made similar findings in a long-term study of >200 patients with low risk factors for SARS-CoV-2 mortality (as per obesity/hypertension / diabetes/heart disease/hospitalization post-acute infection), and concluded that a subset even of low-risk young individuals still reported evidence of these same long-term symptoms (see also [42,43]. This too is consistent with a study from the Netherlands of ~90 pediatric patients with evidence for persistent of fatigue, dyspnea, and concentration difficulties, leading to severe limitations in daily function, and independently Daitch, et al., have reported that age was not an independent predictor of Long COVID symptoms [44,45]. There may be a caveat to the story in the pediatric population however, in that it is not clear if the multisystem inflammatory syndrome in children (MIS-C) which is seen post-acute infection is reflective of a unique age-related immune response, precluding simple comparison with an adult population [46]. A more recent review of risk factors associated with long-COVID following acute SRAS-CoV-2 infection can be found in a review by Hill, et al., [47]. There is nevertheless some consensus in the literature that following an infectious episode, ME/CFS, Fibromylagia and long-COVID all present with markedly similar and vague symptoms of fatigue, concentration defects and mood disorders, and with quite similar degrees of prevalence.

Pathophysiology of long-COVID

As noted above, the pathophysiology underlying ME/CFS and similar syndromes remains an enigma. A review of multiple bibliographic databases concluded that while long-COVID might be (uniquely) associated with long-term organ damage due to acute-phase infection, many specific mechanisms activated/disrupted following initial infection may be contributory factors in the absence of clear evidence of organ damage, including those pertaining to the autonomic nervous system, immune dysregulation, auto-immunity, endothelial dysfunction and occult viral persistence [48]. All of these have also been suggested as co-factors in the etiology of ME/CFS (see above and [5,8,35,49]).

Evidence for viral persistence and chronic antigen stimulation: The main concepts used to explain long-COVID have centred on the longer-term effects of acute virus-induced tissue dysfunction or virus-induced autoimmunity [50]. An alternative hypothesis posits that a latent chronic infection could be responsible for at least some of the symptoms, consistent with evidence that SARS-CoV-2 genetic material, but not necessarily infectious agents, can be detected in some individuals for some time following resolution of overt respiratory disease [51,52]. Thus a sustained inflammatory response caused by the persistence of SARS-CoV-2 in organs/tissues and/or an autoimmune-type mediated reaction following chronic viral exposure are consistent with this hypothesis [53]. Galan, et al., reported on the possible usefulness of a panel of immune markers in subjects with symptoms some 50 weeks post-acute infection, compared with those recovering within 12 weeks with minimal/no sequalae, and reported such individuals had increased levels of functional memory cells with high antiviral cytotoxic activity (including $CD8^+$ TEMRA cells, CD8 ± TCRγδ+ cells, and NK cells with CD56+CD57+NKG2C+ phenotype) along with enhanced levels of $CD4^+$ Tregs and increased expression of the exhaustion marker PD-1(programmed cell death protein 1) on CD3 T cells [54]. Such markers were included in an algorithm which predicted inclusion into the long-COVID group with 100% accuracy. Newell, et al., similarly concluded that there was evidence for a potential role for persistent virus and autoantigens in this syndrome, as well as the contributions of unresolved inflammation and tissue injury, with some data suggesting, as predicted, that successful development of immunity post the acute infectious stage might reduce such symptoms [55]. In contrast, while there is controversial evidence that vaccination might contribute to a decrease in susceptibility to acute infection, or symptoms thereof, there was no evidence that it played any protective effect in protection from long-COVID symptoms, consistent with the notion that the pathophysiology of the two presentations was quite distinct [56-58]. It may also reflect the possibility that vaccination itself can contribute to long-COVID (below).

Innate and other immunological factors which are associated with/may contribute to long-COVID disease: There are a number of anecdotal reports of clinical responses to Histamine Receptor Antagonists (HRAs) in affected patients, suggesting a histamine-dependent mechanism with mast cell activation. Supporting this hypothesis, a study by Weinstock, et al., of ~135 subjects with long-COVID concluded that these latter had many of the features of individuals suffering from mast cell activation syndrome [59]. The notion that T cell regulation of mast cell activation is perturbed in such individuals was explored by Glynne, et al., who examined T cell subsets in 50 subjects with persistent clinical symptoms up to 400 days post-acute infection, finding that long-COVID subjects had reduced $CD4^+$ and $CD8^+$ Effector Memory (EM) cell numbers and increased PD-1 expression on central memory (CM) cells (see also above), while asymptomatic subjects had reduced $CD8^+$ EM cells only and increased CD28 expression on CM cells [54,60]. Consistent with the mast cell activation hypothesis, >70% of symptomatic individuals improved with HRAs, though there was no discernible difference in T cell profiles of this who did/did not respond to HRAs.

Other groups have focused on the relevance of oxidative stress in the pathophysiology of acute/chronic infection with SARS-CoV-2, arguing that since inflammation and oxidative stress are mutually reinforcing to contribute to a systemic hyperinflammatory state and coagulopathy, then aggressive courses of anti-oxidative substances, with associated anti-inflammatory, endothelial-restoring, and immunomodulatory effects might be helpful. There is some supportive evidence for a role of iv high dose vitamin C in multiple studies exploring oxygenation, evidence for a decrease in inflammatory markers, and a faster recovery, subjects infected acutely with SARS-CoV-2, but to date no role for this has been reported in terms of amelioration of fatigue, cognitive disorders, pain and depression in those with long-COVID [61]. More recently Garcia-Abellan, et al., compared serological, T-cell immune responses and ANA (anti-nuclear antigen antibody) titers of patients with long-COVID syndrome of 1-year duration (14 of 154 patients previously hospitalized for infection) [62]. They observed that persistent symptoms of asthenia, myalgia and memory loss/difficulty with concentration were more pronounced in those with a lower frequency of neutralizing viral antibodies, increased ANA titres and levels of inflammatory markers (C reactive protein, CRP). Seeble, et al., came to a similar conclusion regarding a potential “marker” role for this increased incidence of ANA titres in a study of 96 subjects infected with SARS-CoV-2, and followed for 12 months post infection [63]. ~75% of subjects reported at least some issues with reduced exercise capacity/fatigue (~50%), dyspnea /concentration issues (~40%), and sleeping (~25%). ANA titres were >1:160 in ~40% of subjects at 12 months, and neurocognitive issues were reported to be more common in those with titres >1:160 than in those with titres below 1:160. There was no correlation of neurocognitive issues with SARS-CoV-2 antibody levels. Son, et al., have also reported on the association of Autoantibodies (ANA) and pro-inflammatory cytokines (TNF,IL-1) with patient-reported symptoms of fatigue and dyspnea at 12 months post COVID infection, and found a positive correlation of persistent symptoms with ANA titres and TNF levels, though whether these represent causal associations or not was not explored [64]. Uncontrolled inflammatory cytokine production has long been thought to be a primary causal influence in the pathophysiology of acute SArS-CoV-2 infection [35]. The evidence for increased ANA titres in long-COVID suffers is very reminiscent of observations made for ME/CFS, where again no clear evidence for causality has been documented [65].

Neurological issues associated with long COVID: The presence of neurological manifestations (symptoms, signs or diagnoses) both at initiation and during SARS-CoV-2 infection is associated with an increased morbidity/mortality, though the pathophysiology behind this remains unclear, as does any phenotype which might predict a post (acute) SARS-CoV-2 or long-COVID neurological syndrome [66]. In

contrast, Mirfazeli, et al., suggested that constitutional neuropsychiatric symptoms in the acute phase might be predictors of debilitating long-COVID symptoms such as chronic fatigue syndrome and cognitive deficits, implying some linkage between the etiology of the two disorders. It is known that SARS-CoV-2 infection triggers a wave of inflammatory cytokines which can, amongst other effects, induce endothelial cell dysfunction, resulting in coagulopathy and increased risk stroke/thrombosis [35,67]. In addition, inflammation of the endothelium would be predicted to destabilize atherosclerotic plaque and induce thrombotic stroke. Other groups have reported independently on the evidence for chronic endothelial dysfunction as a significant factor in the risk of development of fatigue, chest pain, and neuro-cognitive difficulties in a cohort of over 600 affected subjects (from a total of 800 studied) with long-COVID syndrome [19,68,69]. Even hemorrhagic stroke may be associated with COVID-19 following a reduction in Angiotensin Converting Enzyme-2 (ACE-2) levels after infection, which can produce imbalance of the renin-angiotensin system manifested eventually as inflammation and vasoconstriction. A unifying pathophysiological mechanism of many of the other prominent disorders, including "brain fog", depression, amnesia etc. remains unclear [67]. One hypothesis is that they may reflect chronic effects of poor oxygenation of the brain (from pulmonary injury by SARS-CoV-2), or even a direct invasion of the CNS by the virus or breach of the blood-brain barrier by systemic inflammatory cytokines released during infection [70-72]. A recent study reported evidence for altered vascular transformation biomarkers in long-COVID patients, studying multiple blood biomarkers of vascular transformation, including ANG-1, P-SEL, MMP-1, VE-Cad, Syn-1, Endoglin, PECAM-1, VEGF-A, ICAM-1, VLA-4, E-SEL, thrombomodulin, VEGF-R2, VEGF-R3, VCAM-1 and VEGF-D and found that a combination profile of ANG-1/P-SEL had excellent sensitivity and specificity for long-COVID status ($P<0.0001$), implying a value not only in diagnosis but in therapy [73].

Correlation of long COVID with vaccination: If long COVID is attributable to a host reaction to viral antigen presentation (acute/chronic) it seems obvious to question whether even vaccination itself may induce such symptoms in otherwise healthy individuals. We have argued at length that many of the vaccines introduced for general use were "rushed to the market" without detailed review of any long-term adverse effects, or even with any knowledge of the host resistance mechanism(s) by which they might be used acutely in a protective vaccine strategy [36,74]. As an example, the failure to acknowledge that mucosal immunity has long been known to be of paramount importance in protection from respiratory virus infection, with only recent characterization of the value of vaccines directed to promote such immunity, is a travesty in scientific and public health terms [75]. There are a number of reports of autoimmune phenomena in subjects following SARS-CoV-2 vaccination see also conclusion below [76]. Finally, we highlight a recent manuscript by Cipelli, et al., discussed, in which the blood of a cohort of over 1000 symptomatic subjects seen following anti-SARS-COV-2 mRNA injections from either Pfizer/BioNtech or Moderna, which documented clear evidence of: "abrupt changes…in the peripheral blood profile of 948 patients (which) have never been observed after inoculation by any vaccines in the past according to our clinical experience [77,78]. The sudden transition, usually at the time of a second mRNA injection, from a state of perfect normalcy to a pathological one, with accompanying hemolysis, visible packing and stacking of red blood cells in conjunction with the formation of gigantic conglomerate foreign structures, some of them appearing as graphene-family super-structures, is unprecedented. Such phenomena have never been seen before after any "vaccination" of the past. In our collective experience, and in our shared professional opinion, the large quantity of particles in the blood of mRNA injection recipients is incompatible with normal blood flow especially at the level of the capillaries. As far as we know such self-aggregation phenomena have only been documented after the COVID-19 mRNA injections" [77].

Given the genetic heterogeneity of the human population as stressed by Wilyman, with implications discussed further elsewhere, it is not surprising that mass vaccination, using a "one size fits all" approach, is fraught with such complications and multiple adverse effects (see also [79-81]).

A recent study of a large Scottish cohort performed with previously infected and non-infected subjects concluded that while previous symptomatic infection was associated with a poorer quality of life and multiple (long term) symptoms including breathlessness and confusion, asymptomatic infection was not associated with adverse outcomes and the suggestion was made that vaccination was associated with a reduced risk of symptoms (but see also [54,55]). In marked contrast, no differences in onset of acute SARS-COv-2 symptoms at hospitalization, and long-COVID symptoms six months after hospital discharge, were found between 109 vaccinated (BNT162b2 (Pfizer-BioNTech)) and 92 non-vaccinated groups of subjects [83]. No specific risk factor for any long-COVID symptom was identified for either group. However, the authors acknowledge limitations in these conclusions, namely: "that they are applicable only to previously hospitalized COVID-19 survivors infected with the Delta variant and vaccinated with the BNT162b2 ("Pfizer-BioNTech"); that the study has a very limited sample size, and the vaccinated patients were older than those non-vaccinated, as expected since vaccination strategies were initially focused on vulnerable, e.g., older, individuals, although there were no reported differences in COVID-19 associated-onset symptoms at hospital admission (except for anosmia) seen between vaccinated and non-vaccinated patients; and that they evaluated the impact of COVID-19 vaccine only when administered before the infection, not post infection, and included as "vaccinated" individuals only those who had received two doses of vaccine (individuals who had received just one dose were considered as non-vaccinated). Importantly they did not collect COVID-19 severity or serological biomarkers of inflammation at hospital admission or follow-up, and no attempt was made, given the nature of the study design, to explore the evolution of post-COVID symptoms, thus clouding the attribution of symptoms at six months after hospitalization solely to SARS-CoV-2".

As discussed in detail elsewhere, most of the vaccines used for protection from SARS-Co-V2 use either mRNA or an adenovirus vector to express the spike protein, or deliberately administer recombinant spike protein [36,84]. The aim is that this protein, a major factor involved in viral entry to mammalian cells, will be recognized by the immune system leading to the production of neutralizing antibodies [85]. Theoharides has provided a timely review of many of the factors attributable to vaccination which might help reveal the pathogenesis of long-COVID [86]. Perivascular inflammation has been observed in the brains of deceased patients with COVID-19; other studies have shown both that the spike protein can damage the endothelium in an animal model (through a mechanism involving ACE2 destabilization/downregulation, and that in an *in vitro* model, it disrupts the Blood-Brain Barrier (BBB); spike protein can cross the BBB to induce perivascular inflammation [87-90]. Furthermore, the

spike protein shares antigenic epitopes with multiple human molecular chaperons (very interesting), thus essentially running the risk of triggering an autoimmune reactions [76,91]. Spike protein has also been shown to activate Toll-Like Receptors (TLRs), causing release of inflammatory cytokines [92]. There are even reports that some antibodies produced against the spike protein are not neutralizing but can change the conformation of the protein, leading to improved receptor binding and perhaps facilitating entry to/expression on brain tissue cells, in turn leading to augmented induction of localized inflammatory cytokines [93]. Since neutralizing antibodies themselves would not cross the BBB this would provide a mechanism for unfettered neuro-inflammation and potentially induction of CNS symptoms in long-COVID.

Given the number of reports on the effect of inflammatory cytokines on many of the features reported for long-COVID, ME/CFS, it seems worthy of acknowledgement that induction of these, whether by infection or vaccination, and following either innate immune induction or activation of (T cell mediated) acquired immunity, may be a primary factor implicated in the subsequent pathophysiology of such diseases. As noted earlier, the prevailing (immune) emphasis on the induction of autoantibodies may be explained by the hypothesis that levels of such antibodies may reflect a secondary (non-causal) event in individuals also susceptible to production of autoantibodies, with the "prime mover" being a triggering of high inflammatory cytokine production. Given the lengthy history of stimulation of cytokine production by both adjuvants incorporated into vaccines, and/or by the (novel) use of mRNAs as vaccine components, we wonder also whether vaccination itself is a risk factor for long-COVID, particularly in susceptible individuals (e.g those producing high levels of such cytokines on *in vitro* exposure to poly I:C (Polyinosinic polycytidylic acid); MPLA (Monophosphoryl lipid A) etc. [94-97]. There has been, to our knowledge, no study exploring the effects of different vaccines/different adjuvants or even adjuvants alone on induction of any of the symptoms discussed above in either ME/CFS or long-COVID.

We have argued at some length that the current syndrome associated with the moniker long-COVID is likely a manifestation of the same symptom complex described over 30 years ago as post viral fatigue syndrome, and more recently as ME/CFS [5,98]. The pathophysiology of this disorder remains an enigma, though there is, as detailed above, evidence for an increased susceptibility in subpopulations which point to potential underlying behavioural, physiological and immunological risk factors. This in itself is intriguing given that following the draconian way in which societies everywhere were prepared to conform to novel mass social isolation, restricted work patterns and mandated medical care (ill-tested vaccines), an overall general increase in psychiatric pathology has been seen worldwide [74,99,100-107]. In addition, many reports exist for an increase in subtle signs of autoimmune disorders in individuals either infected and/or vaccinated with SARS-C0V-2 [76,108-110]. Given that at least some of these affected individuals suffer not from the outcome of SARS-CoV-2 infection per se, but from societal responses to infection (isolation; vaccination) these should be classified as iatrogenic diseases, albeit (presumably) in an at-risk population. This conclusion is very sobering both in terms of the recent past, and how we might prepare for the next pandemic when, not if, it comes [111].

Conclusion

This thought is echoed by Thucydides, the Athenian historian of the 5th century BCE, who can arguably be recognized as one of the first epidemiologists charting, with an attention to detail that astonishes us even today, the Plague of Athens (430BCE) which claimed the lives of an estimated one third of the Athenian population. While Thucydides describes the epidemiology of the disease and its symptoms in the greatest detail, he never hazards a guess as to its origins, which remain forever unknown. In this respect Thucydides exhibits the qualities of an objective scientist as well as historian, differing from his elder colleague, Herodotus, who attributed the plague to the "will of the gods". Thucydides further surmised: 'It will be enough for me (us) if these words are judged useful by those who want to understand clearly the events which happened in the past and which (human nature being what it is) will, at some time or other and in much the same ways, be repeated in the future'.

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