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REVIEW ARTICLE

Links between COVID-19, long COVID, and neurodegeneration: The role of glycosphingolipids

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ABSTRACT

Glycosphingolipids (GSLs) play major roles in viral infections by mediating viral entry and egress from cells in lipid rafts; however, GSLs are also important in neurodegenerative diseases. The role of GSLs in acute COVID-19 infection is critical but remains less-studied in the sequelae of long COVID (post-COVID condition); because the same enzymes that regulate GSL metabolism are critical for viral entry and exit, neuromuscular junctions, neurological function, and cellular metabolism, it is important to determine whether long COVID may increase the risk of subsequent neurodegeneration. SARS-CoV-2 infection alters lipid metabolism and oxygen use and can bind to and modify the expression of neurotrophic GSLs such as GM1 ganglioside. GM1 (N-acetylneuraminic acid) is human-specific and probably evolved as a result of a pandemic 3−2.5 million years ago that drove its selection. GM1 functions as a coreceptor with angiotensin-converting enzyme 2 for SARS-CoV-2 while also being a neurotrophin. Viral multiplication takes place in the endoplasmic reticulum/Golgi apparatus, where GSLs are synthesized. This review defines the complex interaction between viruses, GSLs, and neurodegeneration, which provides new perspectives on the interlinked metabolic changes. A European working group has been set up to assess the risks of neurodegeneration with long COVID, based on potential GSL-mediated mechanisms.

Significance Statement: The SARS-CoV-2 pandemic has resulted in a large number of subjects living with long-term consequences (long COVID). Glycosphingolipids and gangliosides are involved in both viral infections and neurodegeneration; hence, it is important to evaluate whether long COVID may increase the risk of neurodegeneration via this route. This study is the result of a European consortium formed to evaluate this possibility.

I. Overview of long COVID

This review was conducted by a consortium commissioned by the European Union through a JPND grant and has reviewed current evidence on whether COVID and long COVID can increase the incidence of neurological disease by changes in glycosphingolipid (GSL) metabolism. This is a critical question because even a small increase in incidence may have important effects on healthcare systems, when COVID-19 has infected a larger number of people. In the United Kingdom, 1.9 million people may have experienced long COVID (2.9% of the population); an estimated 762,000 may continue to report symptoms 2 years postinfection, with around 1 million working days lost to long COVID (prevalence of ongoing symptoms following coronavirus [COVID-19] infection in the UK: March 30, 2023). As an example of the interplay between viral infection and neurodegeneration, Epstein-Barr virus infection has been shown to increase the risk of multiple sclerosis 32-fold.[1,2]

This review does not aim to cover all the research into the symptoms and mechanisms of long COVID (40,000 long COVID references and >3000 PASC references in PubMed, June 2025), but reviews data implicating the potential role of GSLs in SARS-CoV-2 infection and long COVID and risks of neurodegeneration, with a particular focus on metabolic changes.

COVID-19 has a plethora of symptoms and differential age-related severity, with a significant proportion of infections leaving debilitating symptoms (long COVID, PCC, post−COVID-19 conditions, PASC, and postacute sequelae of SARS-CoV-2 infection[3]), which we will refer to as long COVID.[4] Persistent cognitive dysfunction (brain "fog," functional cognitive disorder), chronic fatigue, myalgia, and postexertional malaise, with orthostatic intolerance are particularly marked, but there is a very broad spectrum of symptoms (200 across 10 organ systems).[5] Long COVID is a multisystem condition, with varying severity, depending on the intensity of symptoms during infection, the number of repeat infections, the degree of pulmonary involvement, and whether patients were hospitalized. Multiple papers have described neurological and/or psychiatric involvement,[6–15] and as many as 65 million individuals were proposed to have long COVID worldwide.[11] Seven percent of US adults have experienced long COVID,[16] with 23% of vaccinated adults reporting at least 1 symptom 2 years after infection with the delta variant.[17] Hence, the potential long-term healthcare consequences represent a major healthcare burden.

Nevertheless, there has been a decline in the incidence of long COVID with time since the peak of infections in 2020. In a US census (April–May 2024), 8.9% of patients (10.3% female and 7.3% male) who had been infected reported continuing symptoms of long COVID, with peak ages of 30–59 years old (https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm). However, this has declined from 18.9% (22.6% female and 14.5% male) in June 2022. However, the more prolonged period of analysis since the start of the pandemic has allowed more precise conclusions to be drawn. In the US veterans study, 131,161 survivors of the first infections (ie, unvaccinated) were followed over 3 years: nonhospitalized patients were at an increased risk of death for the first year, but hospitalized patients were at risk over the 3-year period.[13] This important study showed the major effect of hospitalization with incidence rate ratios (IRRs) of myocarditis of 20.3, and myopathy of 10.4. However, in a study of neuropsychiatric symptoms in 475 patients who had been hospitalized (C-Fog study, a part of the PHOSP-COVID cohort), mild depression, anxiety, and cognitive deficits were still present after 3 years, with ~22% showing severe symptoms; depression, anxiety, and fatigue increased from 6 to 36 months.[14] A review of the multiple cognitive domains affected in long COVID showed great heterogeneity, implying generalized dysfunction.[18]

Hospitalization for COVID increased the IRRs for Alzheimer disease (AD) at 1 (2.47), 2 (1.86), and 3 (1.76) years, although for nonhospitalized patients, the IRR was only slightly increased in the first year (1.22). The IRR for Parkinson disease (PD) was only increased at year 1 in hospitalized patients (1.92).[1] In a large study, no common laboratory measure, of 25, could distinguish between patients with symptoms of long COVID and previously infected subjects without symptoms, although GSLs were not assessed.[19] In the large US C4R cohorts, the likelihood of nonrecovery by 90 days was 1 in 4 in early infections and 1 in 5 after Omicron infection; vaccination also helped recovery: risk factors were related to factors causing severe infection, with women more likely than men to suffer long COVID.[20] The C4R and RECOVER cohorts are crucial for future research, as is the PHOSHP-COVID cohort.[21] Hospitalization with COVID-19 has been associated with a subsequent wide range of neurological and psychiatric disorders, but, in an important distinction, the risks of subsequent sequelae in those submitted to intensive care were not worse than for other disorders requiring intensive care.[22] There is also a dissociation between long COVID symptoms and the severity of the acute infection.[21]

A subcortical, speed of processing-predominant, cognitive impairment ("brain fog") is a significant symptom in long COVID, with evidence of not only impairment in those hospitalized patients in intensive care but also prolonged symptoms and recovery in those not hospitalized.[23–28] Changes in brain structure have been reported in long COVID,[8] and brain injury in COVID and influenza has been associated with immune responses to infection.[25] However, neuropsychiatric symptoms were not associated with the neuronal injury markers, neurofilament light, glial fibrillary acidic protein, and total tau protein.[29] Inflammation was present in multiple brain areas in 12 patients, compared with 43 controls, assessed by imaging with [^{11}C]PBR28, a peripheral benzodiazepine receptor ligand, and was correlated with the elevation of 8 markers of vascular integrity.[30] In this respect, frontal striatal glucose metabolism, measured by fluorodeoxyglucose positon emission tomography, did not differ between long COVID patients with fatigue and COVID-recovered subjects, whereas there were clear reductions in multiple sclerosis patients with fatigue.[31] Frailty is a common factor in long COVID, associated with invasive mechanical ventilation, age, and social deprivation, especially in women.[32]

Although there are clear differences in severity from the first wave of COVID-19 in unvaccinated populations, later cases may still be severe and life-changing.[4] In this respect, COVID-19 was associated with more severe outcomes and higher long-term mortality than influenza and respiratory syncytial virus in a cohort of 141,000 nonhospitalized US veterans.[33] The main fatalities from COVID-19 infection following hospitalization involve lung fibrosis, increasing oxygen requirements, and intubation, but recovery from intubation from other infections is also associated with multiple sequelae.[34] Lung abnormalities are present in ~11% of people discharged from hospital following COVID-19,[35] and lung fibrosis can lead to progressive deleterious lung changes. The most extreme case of fibrosis is idiopathic pulmonary fibrosis, which is unremitting. Although, at present, the exact fate of patients with pulmonary involvement following long COVID is not clear,[36] long-term lung dysfunction is a result of pulmonary fibroproliferation, driven by redox imbalance, and the severity was related to survival[37] (reviewed in a previous study[38]), with fibrosis as a common mechanism.[39] Scarring may be reduced by the antifibrotic agents nintedanib and pirfenidone (or deuterated pirfenidone), which are under clinical trial for idiopathic pulmonary fibrosis, and fibrotic lung disease after long COVID, with some beneficial effects when administered after hospitalization.[39–45] Even with normal lung computed tomography (CT) scans, pulmonary efficiency may be reduced in long COVID.[46] As pulmonary fibrosis is severely debilitating, with long-term consequences, usually arising post-hospitalization, it has been proposed to separate this class of patients with long COVID, but there are conflicting views. Long-lasting muscle loss is classically associated with anesthesia and hospitalization, and long COVID is associated with reduced muscle strength[47] and muscle loss posthospitalization.[48] The metabolic effects on heart and brain may be due, partially, to the effects on skeletal muscle, as recent work has changed long-held views on the role of lactate in metabolism, as lactate produced in muscle may fuel heart and brain metabolism, modifying lipid metabolism[49] (see below), and lactate metabolism is markedly changed in long COVID.[50,51]

A. Nasal penetration and viral persistence following SARS-CoV-2 infection

Neuronal infection by SARS-CoV-2 has been studied in the nose by P-M Lledo's group, showing that in hamsters, all SARS-CoV-2 variants are neuroinvasive, but anosmia was an independent phenomenon: the virus may remain in the nose for long periods.[52,53] Stein,[54] in an autopsy study of 44 patients who died of COVID-19, found that SARS-CoV-2 RNA is widely distributed and present in the brain early in infection, and in 1 patient, as late as 230 days following disease onset, albeit without major signs of inflammation (except in respiratory tissue). Furthermore, SARS-CoV-2 was found in peripheral tissue, but not in plasma. SARS-CoV-2 infection of mice expressing human angiotensin-converting enzyme 2 (ACE2) results in brain infection and microglial activation, with NLRP3 inflammasome activation, caused by the SARS-CoV-2 spike protein. Activation could also be activated via NF-κB, implying roles for adenosine-5-triphosphate and α-synuclein.[55] Thus, long COVID may be associated with long-lasting viral load in some tissues, although not readily detectable in blood.

Furthermore, viral infection causes marked changes in cellular metabolism in infected cells, as the virus attempts to optimize conditions for replication by increasing aerobic glycolysis (Warburg effect) and capturing lipids for their envelopes, in the endoplasmic reticulum or the Golgi apparatus.[56,57]

Slow viral clearance or remaining reservoirs of virus have been proposed as potential reasons for prolonged symptoms in some with long COVID.[58] Slower clearance rates after acute infection have been associated with a greater number of symptoms following long COVID.[59] A systematic review of which treatments of acute COVID impacted long COVID symptoms proposed that antiviral treatment was beneficial (odds ratio [OR], 0.61, $P = .0002$),[60] implying better viral clearance; however, data are limited, and there is no evidence to inform clinical practice at the current time. Early intervention with paxlovid (nirmatrelvir/ritonavir) has been associated with reducing smell and taste disorders in long COVID[61] and reducing later risk of stroke and mortality.[62] However, although paxlovid is approved in the treatment of acute COVID, 2 trials (PAX LC and STOP-PASC) have not shown benefit in long COVID versus placebo-ritonavir.[63,64] Reactivation of Epstein-Barr virus may also occur in long COVID patients.[65] The immunological effects of long COVID are correlated with increased antibodies against SARS-CoV-2 and also Epstein-Barr virus,[65] implying that future development of multiple sclerosis should be monitored.

B. Myalgic encephalomyelitis/chronic fatigue syndrome

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has a hazard ratio of 4.93 (95% confidence interval [CI], 3.62−6.71) after COVID infection compared with no infection, with postexertional malaise being the most common symptom.[66] Thus, a significant proportion of long COVID patients fall under the 2015 criteria defined by the National Academy of Medicine for ME/CFS (2015). The main symptoms include fatigue, muscle pain, neurological symptoms, unrefreshing sleep, orthostatic intolerance, profound fatigue (>6 months), postexertional malaise, and cognitive impairment. Three million people in United States experienced ME/CFS prior to COVID, whereas after COVID, there are 15.5 million.[66] There is considerable overlap in these symptoms and long COVID, and most ME/CFS patients report an infectious disease prior to the development of symptoms, such as infectious mononucleosis, sometimes with reactivation of Epstein-Barr virus. Clustering was observed between long COVID and ME-CFS symptoms with 43% of long COVID patients fitting the criteria for ME/CFS,[67] with major overlap between the most severe long COVID patients. Mitochondrial dysfunction may be at the heart of these symptoms.[68−71] This may be part of a primitive stress response and exacerbated sickness behavior.[72] particularly as the severity of acute infection, rather than the specific pathogen, predicts the severity of ME/CFS, and severe ME/CFS symptoms are associated with patients with the most severe long COVID, although severe symptoms can also arise from mild infections. Postexertional malaise is a major symptom of ME/CFS.[73] Hence, it is not easily treated by exercise. However, low-intensity, self-paced swimming has been proposed for some patients,[74] but this is controversial (see below). In this respect, although the symptoms improved over a year in long COVID patients who had not been hospitalized, there was no improvement in this time scale for patients with ME/CFS.[75] The metabolomic response to ME/CFS has been studied, revealing that circulating sphingolipids and glycosphingolipids were the most critically affected, but their levels decreased in ME/CFS[76] and are associated with a hypometabolic state.[71,77] In the largest blood metabolomics study to date, using the UK Biobank (1455 ME/CFS cases and 131,303 controls, and subsequently the USA-based "All of Us" cohort), hundreds of traits differed from controls, indicating inflammation, liver disease, and insulin resistance: the study was able to differentiate these changes from deconditioning, that is, reduced physical activity.[78] However, the study did show markedly reduced circulating sphingomyelins, which are precursors for ceramide.[78] Furthermore, serum lactate levels are increased in patients with ME/CFS with severe postexertional malaise,[79] and lactate levels are increased in those with long COVID.[51] Thus, ME/CFS reflects a very serious component for some people with long COVID.

The immunological responses in acute COVID are complicated and beyond the scope of this review, although immunological changes in long COVID have been well-described, with cortisol being reliably reduced.[65,80] In long COVID, interleukin-1β (IL1β, IL-6, and tumor necrosis factor-alpha levels can be elevated and correlated with symptoms.[81] Autoantibodies have been reported.[65,82] T cell-macrophage interactions in the lung impair the regeneration of alveolae and drive fibrosis, with CD8+ T cells secreting interferon-γ and tumor necrosis factor-alpha, inducing macrophages to release IL-1β.[83] The authors of the latter study proposed the use of baricitinib and anakinra. Elevated fibrinogen related to C-reactive protein has been associated with cognitive deficits and D-dimer relative to C-reactive protein to cognitive deficits, fatigue, and impact on occupation (PHOSP-COVID study),[84] implying a thrombo-inflammatory etiology in some patients. In the brain, microglial activation has been commonly reported, and elevated plasma and cerebrospinal fluid (CSF) levels of neurofilament light (NfL) and glial fibrillary acidic protein have been reported where neurological involvement was present.[85] The classical antiviral type-1 interferon response in microglia has been shown to be elevated in multiple forms of neurodegeneration and associated with loss of synapses.[86]

C. Recovery after SARS-CoV-1

Long COVID after SARS-CoV-1 caused life-changing febrility with strong metabolic changes 12 years after infection, particularly in lipid metabolism, with elevated lysophospholipids and acylcarnitines, essential for long-chain lipid transport into mitochondria, coupled with changes in glucose and lactate metabolism.[87] Although SARS-CoV-1 appears to have been more severe than SARS-CoV-2, the basic symptoms of this form of long COVID appear similar, but with permanent sequelae in the case of SARS-CoV-1 infection.[88] Some of the sequelae were claimed to have been due to high-dose prednisolone in emergency care[87,89]: the sequelae are both physical, in terms of frailty and physical incapacity, but coupled to major shifts in metabolism.

D. Postviral syndromes

Postviral syndromes are common after various viral infections: a comparison of severity in multiple organ systems up to 18 months after either seasonal influenza or COVID-19 has been performed in large populations (>10,000 influenza and >80,000 COVID-19).[90] This study showed that although influenza caused increased long-term pulmonary symptoms, COVID-19 had an increased risk of death, with an excess death rate of 8.6/100 for long COVID compared with influenza, with COVID-19 increasing the risk in multiple organ systems. Hospital admissions were increased in the postacute phases of both infections, and the increase in risk of specific disorders is major[13,90] and will be covered in the following sections, relating to the implication of GSLs in these disorders. Postacute vaccination syndrome may occur rarely, with malaise and chronic fatigue, and a prevalence of 0.02%.[91]

Viral respiratory infections can reactivate dormant metastatic breast cancer cells in the lungs, via IL-6, leading to severe expansion of previously quiescent cells within weeks of infection: COVID-19 infection increased the odds ratio of cancer reappearance (OR, 1.8,

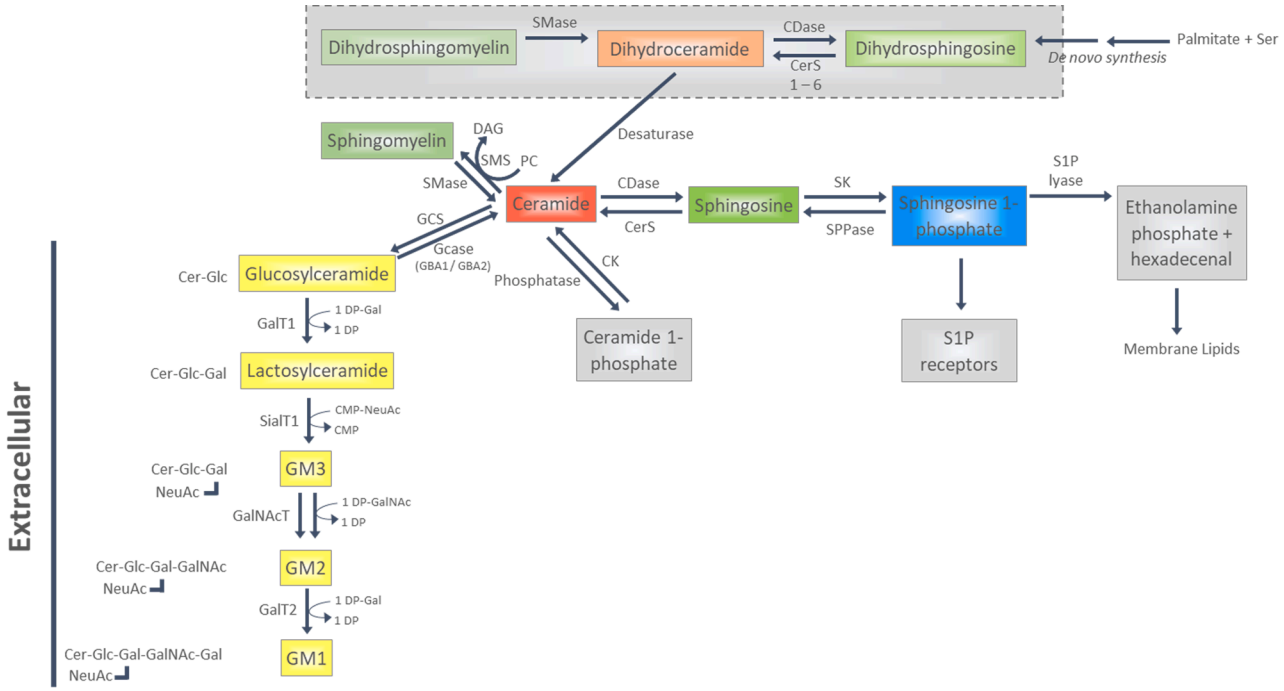

Fig. 1. Synthesis and metabolism of ceramide, glycosphingolipids, and gangliosides, such as GM3, GM2, and GM1, which have the "human" sialic acid Neu5Ac in man. Synthesis de novo is from palmitate and serine via serine palmitoyl transferase, where ceramide levels exert negative feedback. The 6 ceramide synthases (CerS1-6) yield distinct lipid chain lengths of ceramides.[104] The role of dihydroceramides have been recently reviewed.[105] Ceramide is synthesized in the endoplasmic reticulum and transferred to the Golgi apparatus, at ER-Golgi contact sites, by ceramide transport protein (CERT) where ceramide is converted predominantly into sphingomyelin (SM), liberating diacylglycerol (DAG) from phosphatidylcholine.[106] GCS glycosylates ceramides, followed by galactosylation (lactosylceramide) and subsequent addition of galactose and sialic acids, such as Neu5Ac. Alternative pathways are shown in Fig. 2. For further details, see review by Guo.[103] In order to allow the enzymes to access the GSLs and gangliosides embedded in membranes, sphingolipid activator proteins (saposins) are enzyme cofactors and act as "micro" detergents. All saposins are derived from a single precusor, prosaposin.

95% CI, 0.9—3.8).[92] The mechanism for this effect was evaluated in a mouse model of cancer dormancy, whereby mice overexpress *Neu*, a paralog of *HER2*. Virally induced inflammation increased IL-6, and this inflammatory signal stimulated $CD4^+$ cells, which maintained the previously activated cells by repressing $CD8^+$ cytotoxic cells.[92] These authors did not investigate the role of GSLs in their model, but the critical gene for GSL synthesis, glucosylceramide synthase (GCS and *UGCG* gene), is a superenhancer, regulating cell phenotype, essential for natural killer and $CD8^+$ cytotoxic cell function, and GCS is upregulated following viral infection.[93,94] Natural killer and CD8+ cells are essential to maintain breast cancer cell dormancy, which is lost after COVID-19 infection, indicating a potentially powerful new role for GSLs in this serious postviral disorder.

II. Glycosphingolipids and gangliosides

Section 1 has shown how long COVID has multiple, albeit disparate, effects throughout the body, implying that SARS-CoV-2 must interact with powerful endogenous targets; attention has mainly focused on ACE2, cellular transmembrane serine protease 2 (TMPRSS2), and neuropilin-1.[95] However, the entry of enveloped viruses into cells is also dependent on lipid rafts and sialylated glycans and GSLs,[96,97] with GSLs being involved in multiple organ systems (particularly in nervous tissue and cell signaling in general). However, GSLs are understudied because of the combined technical complexity of accurately measuring complex mixtures of glycoconjugates comprising sugars and lipids, in addition to their multistep enzymatic biosynthetic and catabolic pathways.[98] The complexity of polysaccharides dwarfs that of proteins or genes, for example, a pentasaccharide of D-hexoses has 2.6×10^9 possible structures,[99] 1 of which is GM1 ganglioside, a 5-sugar glycosphingolipid that is a critical endogenous neurotrophic factor and represents 17% of the total GSL levels in the brain.[100]

Furthermore, GSLs are chemically stable, forming part of the glycocalyx, controlled by 1% to 3% of the genome, but with immense recognition capacity by viruses. The sugars give age-dependent signatures of individual cells. However, glucosyl hydrolases can increase specific hydrolysis rates by 10^{17},[101] Hence, there is considerable plasticity. The complexity of the lipid chains in the membrane, via variation in chain length and saturation, yielding ~4000 sphingolipids, complements these signatures and is also important in forming membrane subdomains, including the formation of lipid rafts. Lipid asymmetry is important for caveolae formation and driving vesicle formation.[102] Sphingolipids all have a ceramide skeleton, and the 6-ceramide synthases regulate the chain length of the ceramide lipids. The complexity of GSLs is beyond the scope of this review, but synthetic and degradative pathways are shown in Figs. 1 and $2^{103–110}$ and are further well covered by Guo.[103] A critical issue is that GSLs are synthesized in the endoplasmic reticulum and Golgi apparatus (ER/G) but broken down in lysosomes or recycled in the ER/G (Fig. 3). Mutations in lysosomal enzymes lead to the accumulation of specific GSLs and result in a family of rare lysosomal diseases—often presenting with neurodegenerative phenotypes.

A. A crucial role for sialic acids in human evolution and viral infection

Sialic acids (9-carbon sugars), as defined by Svennerholm,[111] cover cell surfaces, forming the sialome, which defines surface complexity and charge, and other aspects of cell signaling.[112] The

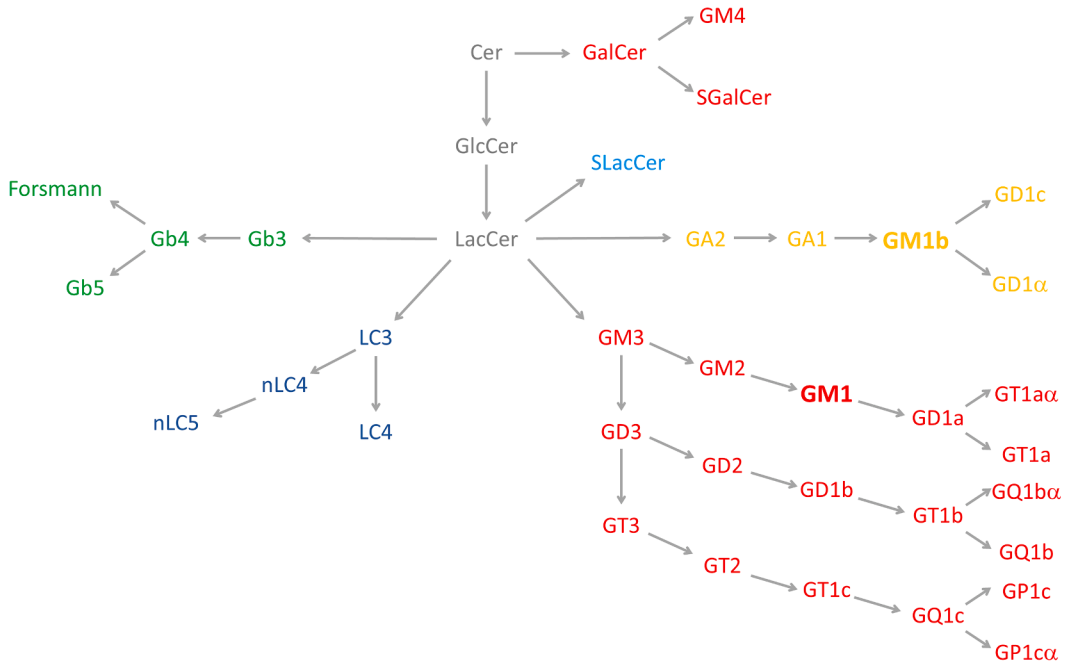

Fig. 2. Schematic synthesis of glycosphingolipids and gangliosides from ceramide via galactosylceramide or glucosylceramide. The most abundant gangliosides in mammalian nervous systems are GM1, GD1a, GD1b, and GT1b. Addition of a sialic acid to a GSL changes the nomenclature to a ganglioside. Nomenclature is according to Svennerholm.[108] The multiple enzymes involved are reviewed in full.[103,107,109]

nomenclature of >90 sialic acids (nonulosonic acids) is established.[113] Sialic acid-containing GSLs (gangliosides) are critical for the entry of multiple enveloped viruses via lipid rafts.[114] The pioneering work of Ajit Varki on sialic acids has emphasized the extreme diversity of this class of compounds, whereby the sugars give incredible complexity, critical for cellular recognition, which is exploited by viruses and bacteria. Sialic acids are also linked to many glycoproteins and sialic acid-binding immunoglobulin-type lectins, which are sialic acid-tipped immunoglobulin chains, crucial for cell-cell adhesion, and involved in multiple immune interactions with high selectivity. Varki defined the genes that generate the sialome, where there are less than 60 genes and more than 10 uniquely human genetic changes.[115] Furthermore, humans have developed a remarkable specificity. Approximately 3–2.5 million years ago, the enzyme cytidine monophospho-N-acetylneuraminic acid hydroxylase (CMAH) became a pseudogene, preventing the synthesis of the sialic acid N-glycolylneuraminic acid (Neu5Gc), resulting in the predominance of the precursor, N-acetylneuraminic acid (Neu5Ac) (Varki, 2010; Fig. 4),[116,117] probably because of a pandemic targeting Neu5Gc that decimated the hominins at that time,[118] providing a very significant selection pressure. Neu5Gc is more lipophilic than Neu5Ac, which will affect binding of Neu5Ac gangliosides to their targets.[119]

Changes in the sialome throughout the body have been postulated to be a major driver in human evolution, at a time when hominins evolved to run and increase brain volume.[120] Eliminating CMAH in mice allows the mice to run further, with marked changes in oxygen sensitivity.[121] The sialic acid, Neu5Ac, is present in many glycans. Coincidentally, humans evolved changes in basal and maximal metabolism to increase maximum oxygen consumption, mL/kg/min (over ~1 million years of evolution), probably by hunting prey by endurance and heat shock while increasing brain size, longevity, and the multiple changes, which, in the presence of modern lifestyles, lead to susceptibility to modern diseases.[120,122–124] Changes in mitochondrial lipid metabolism have been an essential component affecting metabolic efficiency in human evolution,[125] and it is important to note that lipid metabolism is modified in long COVID (see below).

B. GM1, a neurotrophic ganglioside, a key component of lipid rafts, and a target for SARS-CoV-2

GM1 is enriched in lipid rafts, is neurotrophic, and binds to the receptors for nerve growth factor (NGF), tyrosine-kinase receptor A (TrkA), and brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB). Human GM1 is tipped with Neu5Ac, which is a target for multiple viruses, malaria, and the cholera toxin B subunit (CTB), whereas old-world nonhuman primates and most other mammalian species have mainly Neu5Gc.[112] However, the critical importance of Neu5Ac in neuronal function has resulted in a downregulation of CMAH, in varying degrees, in the brains of multiple species.

Lipid rafts are critical for cellular signaling, and consist mainly of sphingomyelin, ceramides, GSLs, and gangliosides, which may be GM1, cholesterol, dipalmitoylphosphatidylcholine, and signaling proteins, essential in cellular signaling (Fig. 5).[126] The 5–25 nm clusters of sphingolipid, cholesterol, and protein that make up a lipid raft are tightly packed because of the ceramide/cholesterol affinity and dipalmitoylphosphatidylcholine/cholesterol affinity, and they rapidly assemble and disassemble. The ganglioside composition changes the structure of lipid rafts and the electronegative potentials, which yield different raft structures between astrocytes and neurons.[127] GM1 binds tightly to cholesterol because of an interaction known as the “NH trick,”[128] whereby the amide group in the N-acetylated sugars counteracts the acidity of the sialic acid, allowing the conical more polar part of cholesterol to associate with the thin apolar shape of the sphingolipids.[128]

However, transglycosylation of cholesterol by nonlysosomal b-glucosylceramidase (GBA2) activation (at the beginning of amyotrophic lateral sclerosis [ALS] denervation[129]) would have a major effect on lipid raft dynamics by reducing glucosyl ceramide

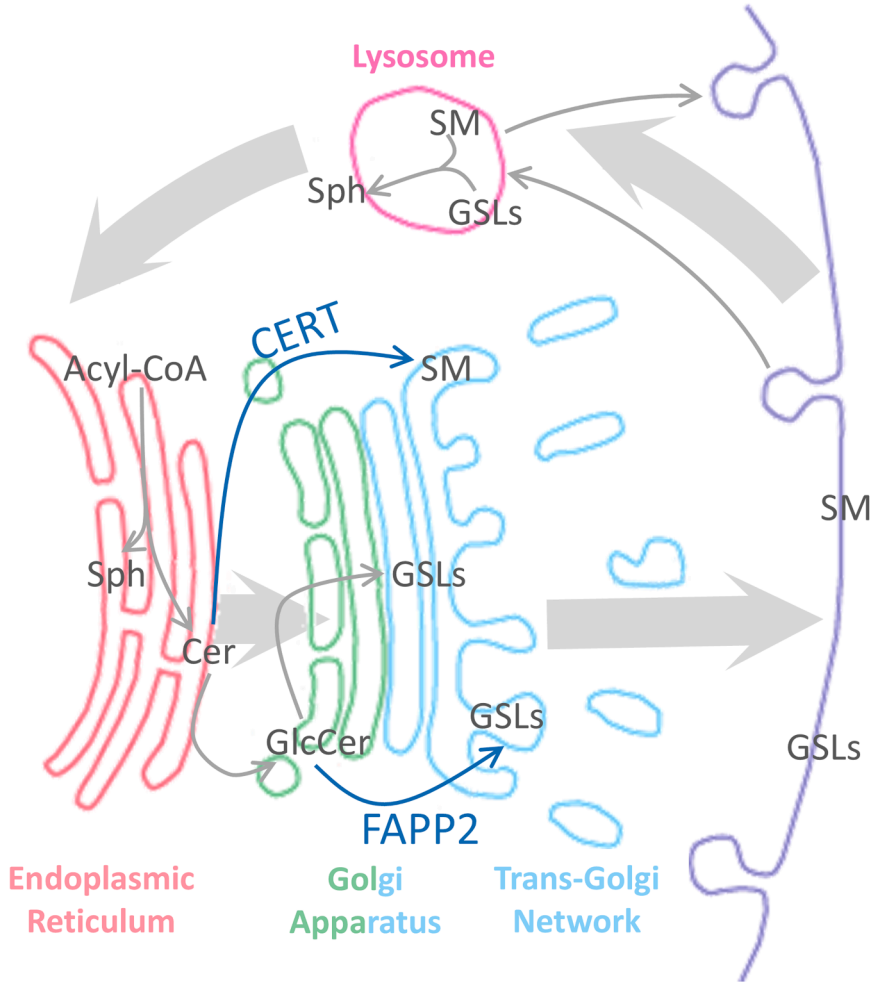

Fig. 3. Localization of the synthesis of glycosphingolipids. Ceramide is synthesized in the endoplasmic reticulum (ER) and GSLs in the Golgi apparatus. A 4-phosphate adaptor protein, FAPP2, is a glucosylceramide transfer protein, important for the synthesis of globo series neutral GSLs in the late Golgi apparatus.[110] Although synthesis of GSLs is in Golgi, they are also transported to the cell surface and are located predominantly in lipid rafts. Most breakdown is in lysosomes, where defects in metabolizing enzymes lead to the specific lysosomal disorders.[103,107,109] Enveloped viruses multiply in, and disrupt, ER and Golgi, disrupting lipid metabolism.

(GlcCer) and GM1, whereas at the same time, glycosylating cholesterol, which would change its hydrophobicity and position in the membrane, affect lipid raft stability.[130] The same arguments can also be made for galactosylation of cholesterol, via GBA2.[131] This would have a major effect on cell signaling as molecular dynamics simulations have been successfully used to study the interaction of various proteins (eg, Alzheimer beta amyloid peptide, plasmolipin, and botulinum toxins) with gangliosides in raft membranes, taking into account the degree of GM1 condensation in distinct raft areas.[132,133] In this respect, the uptake of cholesterol into membranes favors the movement of ACE2 into lipid rafts with GM1, which can then internalize the virus.[134,135]

GM1, being a component of many lipid rafts, enables viral entry via rafts. Human GM1, with Neu-5Ac, is a target for many pathogens, including cholera toxin, malaria, influenza, dengue,[136] and SARS-CoV-2.[137,138] which have evolved to target humans over the last 3 million years.[115] SARS-CoV-2 binds directly to GM1 and GM3, and this may be critical for viral entry, with viruses developing specific ganglioside-binding domains on lateral N-terminal domains of the spike proteins, facilitating coupling with viral targets, such as ACE-2, via receptor-binding domains.[114,128,134,139]

Cholera toxin binding has been used to label lipid rafts and GM1[140,141] (with an affinity of 43 nM[142]), and the crystal structure of the complex between CTB and the terminal sialic acid and adjacent galactose has been published.[143] Although the inhibition of GSL synthesis exacerbates CT toxicity, CT can still induce toxicity in the absence of GM1.[144] Some of this controversy has been resolved in that, in enteric cells, fucosylated GSLs, proteins, or glycans can act as both target receptors (for toxicity) and decoy receptors for CTB.[144–147] Thus, CTB binding cannot be assumed to be a measure of GM1, but the situation is complicated and will depend on the local ganglioside concentrations. Fucosylated GM1 is a target for CTB, and fucosylated GM1 occurs in tumors. However, very little is present on other tissues, allowing the development of antibodies against fucosyl-GM1 for human small cell lung cancer.[148] GM1 is present in very low concentrations in human intestine,[149] being probably excluded because of its high affinity for pathogens. However, GM1 and GD1a (a reservoir for GM1[116]) are mainly located in white matter, brain nuclei, nodes of Ranvier, and neuromuscular junctions (reviewed by Guo[107]), with GM1 predominantly in motor neuron myelin, rather than sensory neuron myelin.[150] The very high concentration of GM1 in the brain, and particularly in myelin, where gangliosides represent 75% of sialic acids[151] means that although there may be other targets, a significant component of CTB binding may be to GM1. Neuraminidases 3 and 4 remove the terminal sialic acids on GSLs and glycan chains,[152] and *Vibrio cholerae* can restructure gangliosides to increase the concentration of GM1. Addition of exogenous GM1 increases CTB binding and susceptibility of cells to cholera (from 17,000 molecules of GM1/cell).[153]

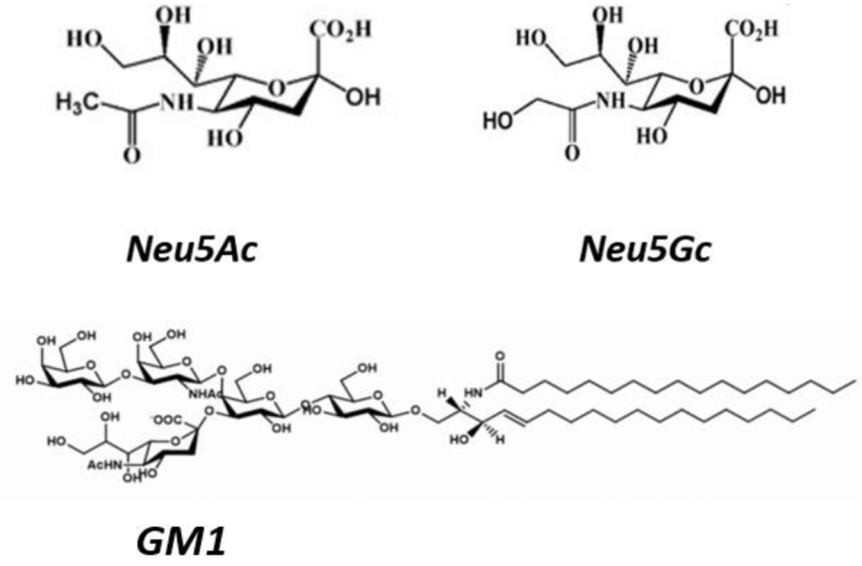

Fig. 4. Structures of the sialic acid, Neu5Ac, and N-glycolylneuraminic acid (Neu5Gc). The structure of the ganglioside GM1 is also shown, in the human form, with the sialic acid, Neu5Ac. Cytidine monophospho-N-acetylneuraminic acid hydroxylase (CMAH) synthesizes the sialic acid Neu5Gc from Neu5Ac but became a pseudogene in hominins ~3 Mya, changing the sialic acid in GM1, and hence, susceptibility to pathogens targeting Neu5Gc. The oligosaccharide portion of GM1 is responsible for much of the neurotrophic aspects of GM1,[116,117] as well as being a recognition site for pathogens.

The SARS-CoV-2 spike protein/receptor-binding domain binds to monosubstituted sialic acid gangliosides, such as GM1 and GM2 (the top hits in a glycan screen, with a similar affinity to heparan sulphate[114]). The relative human specificity of viruses may be partly due to higher affinity for Neu5Ac than Neu5Gc.[154,155] As the lipid rafts will present a negative charge from the sialic acids, SARS-CoV-2 variants have exploited this by evolving an increase in positive electrostatic potential by 6.7-fold from the original Wuhan strain to Omicron XBB[156]: ACE2 is also a very electronegative protein; hence, some of the evolution of SARS-CoV-2 may be considered an exploitation of the coupling of gangliosides in lipid rafts with ACE2.

Modification of the key enzymes (Fig. 1) can have major effects in disease situations. For example, the nonlysosomal β-glucosylceramidase, GBA2, is increased 8-fold in the spinal cord at the earliest disease stages in models of ALS, and its inhibition is beneficial for the preservation of neuromuscular junctions, GSLs, and GM1.[129] Mutations in the lysosomal enzyme lysosomal b-glucosylceramidase (GBA1) cause increases in glycosphingolipids, which are the main genetic cause of Gaucher's disease and PD. Misfolded GCase proteins are retained in the endoplasmic reticulum, altering the lysosomal trafficking of the enzyme and disrupting protein trafficking. Furthermore, α-synuclein itself can lower the enzymatic activity of GCase, and a bidirectional interaction exists between GCase and α-synuclein, which may lead to self-propagating neurodegeneration.[157]

C. Ceramides

The sphingolipid, ceramide, is a critical hub in cellular metabolism, and the genes controlling ceramide synthesis are longevity-associated genes (eg, *lag*1) in yeast, controlling acyl

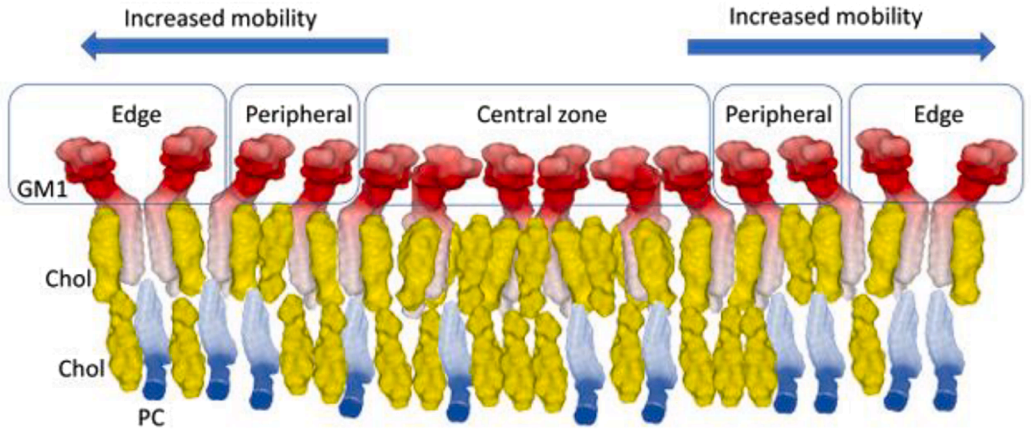

Fig. 5. Schematic diagram of packing of GM1 in lipid rafts (extracellular oligosaccharide portion in red), with denser packing in the central zone (reproduced from Fantini, 2023,[126] with permission). Cholesterol packing to GM1 is allowed by the "NH trick" where the acidic sialic acid is screened by the NH trick (see text). Lipid rafts concentrate many signaling molecules, tightly linked to GM1.and the multiple hydrogen bonds of gangliosides and GSLs are important for their placement. An example is the NGF receptor, TrkA, which has a central core for the ceramide of GM1, and a polar extracellular pocket for the oligosaccharide; hence, GM1 is essential for the incorporation of TrkA into membranes,[116] Multiple pathogens, including the SARS-CoV-2 variants, have evolved specific ganglioside-binding domains for interaction with raft and internalization.[126] Thus, gangliosides and GSLs are critical for both neurotrophins and viral targeting. PC is dipalmitoylphosphatidylcholine.

chain length, autophagy, apoptosis, and aspects of cell metabolism, including the mechanistic target of rapamycin. Ceramidases can lead to increasing sphingosine or sphingosine 1-phosphate, which often counteracts the apoptotic effects of ceramide (Fig. 1). Sphingomyelin is a reservoir for ceramide, being the most abundant sphingolipid, particularly in myelin, with sphingomyelinases generating ceramide (Fig. 1), but the lipophilicity of ceramide is highly disruptive for cell membrane integrity, potentially causing apoptosis. Hence, this reaction is highly regulated, to the extent that ceramide has been referred to as a "wild tiger," with sphingomyelin referred to as a "caged tiger."[158,159]

The release of ceramide into the circulation, depending on the severity of SARS-CoV-2 infection, indicates the power of this reaction (Fig. 6).[160–170] Ceramide has also been shown to play critical roles in neurodegeneration, particularly PD and ALS. The metabolism of ceramide, to sphingomyelin, sphingosine, or glucosylceramide, with the subsequent formation of complex glycosphingolipids, represents major switches in cellular

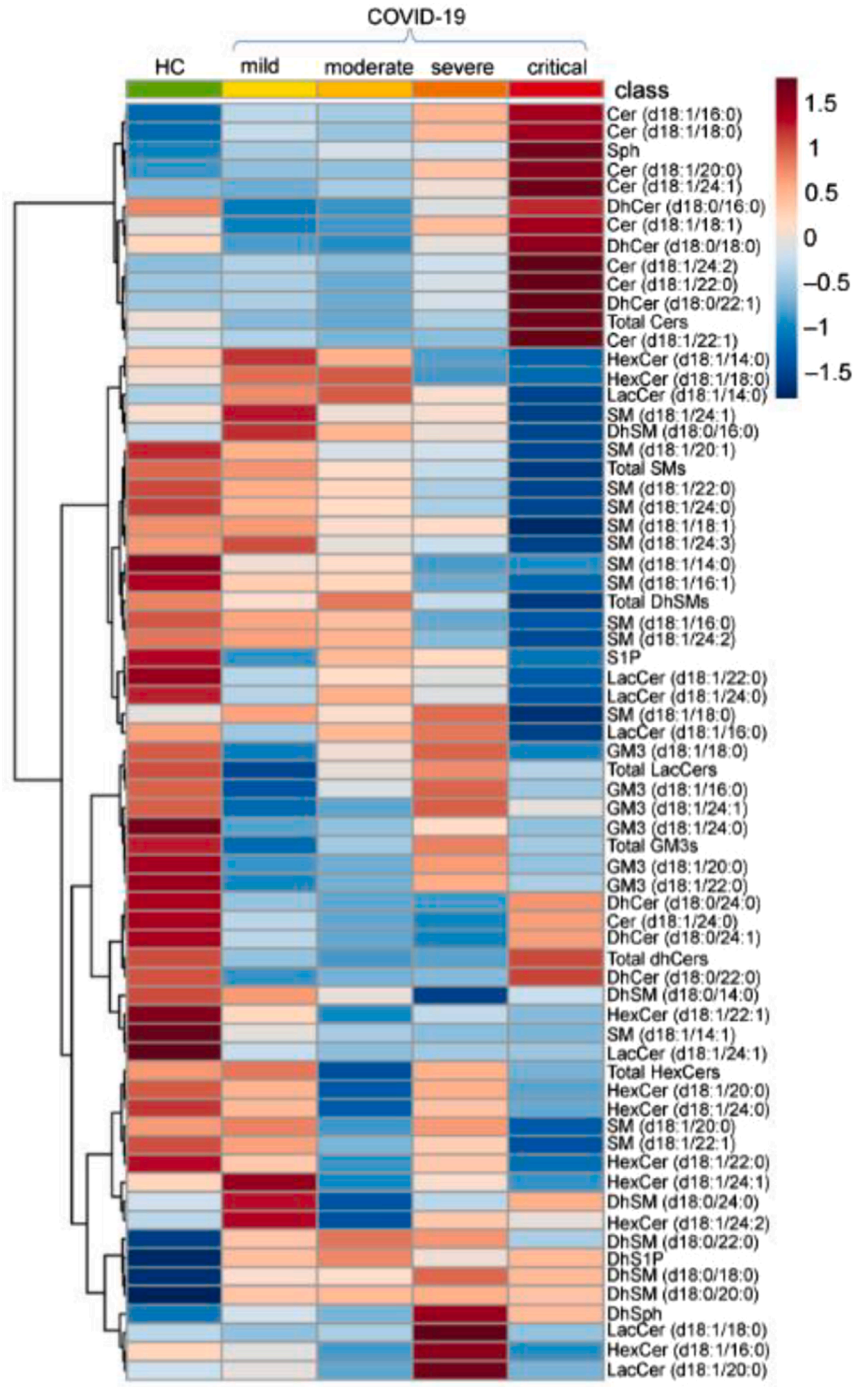

Fig. 6. Heatmap of average abundance of 68 sphingolipids in sera, quantified by LC-MS/MS, in healthy controls (HC) and in acute COVID-19 patients (mild, moderate, severe, and critical). The figure is taken from Obara et al,[160] with permission. Note the mobilization of sphingomyelins (SM) and build-up of ceramides as patients became critically ill. Increases in ceramides such as this have been widely reproduced in severe COVID,[161–169] although reductions in sphingomyelins and ceramide were reported in ME/CFS[170]

metabolism but may also be involved in multiple diseases, including fibrosis, lysosomal diseases, and neurodegeneration.

Sphingolipids, particularly ceramides, accumulate in the muscles of aged mice, and the inhibition of de novo synthesis by inhibiting serine-palmitoyl transferase, using myriocin, counteracts age-induced sarcopenia.[171] Myelination is also dependent on galactosylceramidase, which binds TMEM106-B (a potential receptor for SARS-CoV-2[172]) to create galactosylceramide and its sulfatide derivative.[173]

D. Glycosphingolipids, gangliosides, and viral infections

The multiple pathways involved in the envelope virus infection have been reviewed,[96] pointing out the critical role played by ceramide, glycosphingolipids (GSLs), and gangliosides in all cases of infection by enveloped viruses. Lipid rafts are essential for the entry and egress of viral particles, with sphingomyelinases being critical in terms of the modulation of viral activity. There is thereby interest in testing drugs affecting GSL metabolism in COVID and long COVID (below). GSLs, and particularly their associated sialic acids in gangliosides, are critical for the recognition of all enveloped virus, their binding to their molecular targets on host cells, incorporation via lipid rafts, and replication in endoplasmic reticulum, forming their envelopes from host cholesterol and GSLs.[96,97] For example, influenza virus replication is absolutely dependent on GCS and UGCG and GCase.[174,175] Similarly, zika virus replication is markedly reduced by knockout of GCS and lactosylceramide synthase (B4G5); in contrast, GCS loss did not affect zika binding to cells.[176] Dengue virus envelopes derived from mammalian LLCMK2 cells, and mosquito C6/36 cells showed distinct GSL profiles.[177]

Enveloped viruses replicate in the ER/G, using host cell glycosphingolipids from ER/G to create their membranes, changing host cell lipid metabolism massively, as mitochondria-associated membranes are tethered to ER/G.[178] The severity of acute infection in COVID-19 patients is predicted by serum GSLs (Fig. 6).[160,179] Indeed, GSLs are involved in almost every step of enveloped virus infection of host cells.[96,97] Platelets from COVID-infected patients show elevated levels of GM3.[180] Indeed, the severity of acute COVID-19 infection is correlated with changes in circulating GSLs (Fig. 6) and ceramides, with a corresponding decline in sphingomyelin species. This is a common factor in viral infection of host cells, and the ceramide-to-sphingomyelin ratio was the most prominent change in VeroE6-TMPRSS2 cells infected with SARS-CoV-2.[181] The envelopes of SARS-CoV-2 viruses are surprisingly understudied, compared to their spike proteins, but phospholipids (phosphatidyl ethanolamine, PE; phosphatidyl choline, PC; phosphatidyl serine PS; and phosphatidyl inositol, PI[182]) are present with lower levels of sphingomyelins and ceramide in ratios dependent on the cell type infected (A549 or Vero).[182]

Although there are similarities in lipid and GSL changes post-viral infection, there are also differences depending on the class of virus and between host cell types. The type of infected cells modifies the GSL profile in the viral envelope: for example, the influenza viral envelope is made up of lactosyl ceramide, cholesterol, and some phospholipids derived from the host cell ER membrane.[183] The influenza virus envelope is formed, following budding from lipid rafts and consists of sphingolipids (ceramides) and cholesterol, with an enrichment of sphingolipids (lactosyl ceramide) from GM3. GM3 is broken down by the presence of the specific neuraminidases on the envelope with the role of "deforesting" host cell glycocalyx, allowing entry into further host cells, but which will also affect the envelope GSLs (eg, GM3).[183]

In acute COVID infection, circulating ceramide was very significantly increased in the most severe cases, with marked reductions in sphingomyelins (Fig. 6),[160] whereas in metabolomic studies, in long COVID, changes in sphingolipid metabolism and galactose metabolism were heavily enriched, associated with defects in lactate metabolism and increases in the lactate/pyruvate ratio, together with increases in long-chain acylcarnitines indicating disrupted lipid metabolism and mitochondrial dysfunction.[184]

Viruses remodel lipid metabolism. Active lipid reorganization in the midgut of *Aedes aegypti* mosquitoes aligns temporally with dengue virus replication.[185] In this study, there was an increase in the lipid content, increase in glycerophospholipids, sphingolipids, and fatty acids, which is coincident with the kinetics of viral replication. Elevated GSL levels suggest a diversion of resources during infection from energy storage to biosynthetic pathways. Elevated levels of acyl-carnitines signal disruptions of lipid metabolism and mitochondrial function. How can this be linked to viral multiplication?

III. Convergence of control of glycosphingolipid synthesis, mitochondrial metabolism, and viral replication in the Golgi and endoplasmic reticulum

A central hub in the GSL biosynthetic pathway (glycosylation of ceramide on the outer leaflet of the early Golgi, the first committed step for GSL biosynthesis) and ER-Golgi transfer of ceramide was identified as critical for the replication of enveloped viruses. Dengue and Zika virus infections induce a major stress response in the Golgi associated with viral assembly/secretion.[186] Similarly, both influenza and SARS-CoV-2 remodel the Golgi for their assembly/secretion.[161,187] The impact of SARS-CoV-2 on the ER/unfolded protein response is very significant.[188] SARS-CoV-2 subverts the ER and Golgi for viral assembly, which has been defined by multiple tools, including electron microscopy,[189,190] and this will have marked effects on GSL synthesis.

As ceramide/glucosylceramide is a critical hub enveloped virus replication, certain GSLs are increased by infection. Enveloped viruses cause massive disruption in the ER/Golgi, where GSLs are synthesized, and therefore will disrupt mitochondria-associated membranes (MAMs). The structure of ER-MAMS has been published, and the ER-MAMS are a pathway for lipids to enter into mitochondria; the precise structures mediating the transport of phospholipids between the ER and mitochondria have been defined.[191] ER-MAMS disrupts phospholipid synthesis, phosphatidylserine, and phosphatidylethanolamine, and therefore, mitochondrial lipid biosynthesis will be compromised, as measured by acylcarnitine flux.[192–194] These lipids are markedly modified in PD and ALS—and are modified by SARS-CoV-2 (as described above). In this respect, ER stress has been shown to be critical for mitochondrial dysfunction in *TDP-43* and *C9orf72* models of ALS.[195]

Vance discovered that the PI/PE ratio is critically dependent on the ER-MAMS, and the PI/PE ratio is critical for mitochondrial function.[192,194,196] Phosphatidyl inositol (synthesized predominantly via phosphatidylserine decarboxylase and CDP-ethanolamine pathways) serves as a basis for PE synthesis and consequent phosphatidyl choline (PC) synthesis.[197] AD, PD, and viral virulence have been shown to be accompanied by changes in PE metabolism.[197]

The molecular nature of the effects of SARS-CoV-2 on lipid metabolism is being elucidated. The ORF6 protein binds to lipid droplets via amphipathic helices and links the droplets to the ER (via BPA32 and USE1). ORF6 also binds to the SAMM50 mitochondrial complex to increase lipolysis, thereby increasing β-oxidation[198] and further increasing lipid flux for envelope production.

Host cells may have remarkable differences in their metabolic responses to viral infection. Semliki Forest virus grown in mosquito

C6/36 cells shows a very distinct phospholipid content compared with that grown in hamster BHK cells.[199] Similarly, dengue virus envelopes derived from mammalian LLCMK2 cells and mosquito C6/36 cells showed distinct GSL profiles. Furthermore, zika virus replication is markedly reduced by knockout of GCS and lactosylceramide synthase (B4G5); in contrast, GCS loss did not affect zika binding to cells.[176] Influenza virus replication is dependent on GCS and GCase.[174,175]

IV. Factors involved in age-related decline and susceptibility to COVID-19, and long COVID

A. Human performance, aging, and COVID-19

There is a very precise decline in neuromuscular performance and maximum oxygen consumption, mL/kg/min with age, as assessed by the decline in world records for men and women at 5000 m, which echoes the mortality following acute infection with COVID-19 and influenza, shown in Fig. 7.[200] Thus, the metabolic decline associated with age may exacerbate the metabolic changes associated with viral infection described above. The great precision of the decline shown in Fig. 7 is because age-related world records indicate the best performances of humanity, as the confounding effects of disease are minimized, leaving a decline following a simple exponential,[201] probably resembling increased entropy with aging[202,203] and hence greater susceptibility to multiple types of stressors, particularly COVID-19 infection. Indeed, viral infections such as COVID-19, which affect multiple cell types, have been claimed to accelerate aging[204] and induce senescence. Although long COVID has been claimed to be particularly severe in the elderly population,[205] it is believed that long COVID rates are lower in the younger (18–29 year) and older populations (>65 years) and highest among individuals aged 35–44 years, particularly in women.[206] Furthermore, an aspect of reduced executive function and working memory found in elderly people (age range, 50–96 years) was related to reduced exercise, increased alcohol use, and depression during the first 2 years of the pandemic.[26]

BDNF has been proposed as a key factor in this evolution in the evolution of humans to run ~2.5 million years ago (Mya),[123,207] as

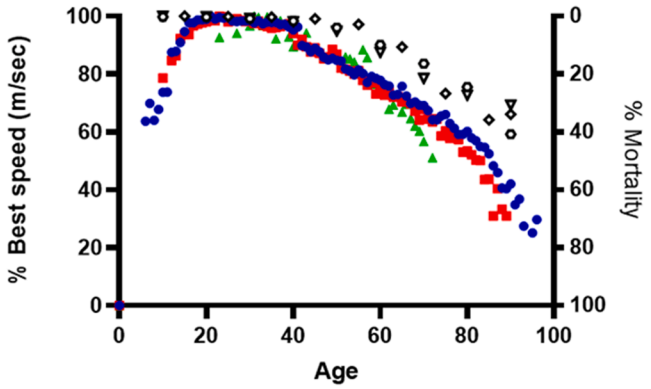

Fig. 7. Speed expressed as a percentage of world's absolute best performance for men (●) and women (■) and for an individual (MS, ▲) as percentage of personal best. Note the almost exact superimposition of curves Records are from the ARRS database (https://arrs.run/SA_O5K.htm) prior to COVID: later records are affected by the availability of carbon-plated running shoes so are not shown. Also shown is the age-dependency of mortality for COVID-19 in the USA (○), and in Italy (◇) in the first year of infection (2020, prevaccination). The age dependency for deaths from influenza and pneumonia in the USA in 2018 (Flu, ▽) is also shown. Viral data are from Centers for Disease Control and Prevention (cdc.gov). Reproduced from Spedding et al[200] with permission.

BDNF is increased by exercise in multiple tissues[208] and is a critical factor for linking neuronal activity and neuroplasticity. The respiratory coupling index of brain mitochondria, a measure of mitochondrial efficiency,[209] is increased by BDNF, via the neurotrophic pathway (TrkB, MEK, Bcl2, and VDAC) but inhibited by IL1β.[210] GM1 activates TrkA and TrkB, the receptors for NGF and BDNF,[211] respectively, and may also release BDNF[212] and mediates antidepressant effects via BDNF.[213] GM1 also has major effects on lactate metabolism in astrocytes.[214] Thus, the interplay of Neu5Ac-GM1 and BDNF may have played a critical role in human evolution via its neurotrophic and metabolic properties, following a viral infection.[215]

B. Virally induced senescence

Galactose is a C4-epimer of glucose, but with a major difference, it is not metabolized for energy directly and thus serves a more structural role in some GSLs, rather than an immediate energy source. For use as an energy source, metabolism of galactose to glucose is mainly via the Leloir pathway. However, disorders of galactose metabolism are associated with senescence. Feeding high levels of D-galactose has been used as a model of accelerated aging in rodents (50–200 mg/kg/day for 6–10 weeks) increasing senescence-associated β-galactosidase accumulation accompanied by aging phenotypes.[216] This model also shows immunosenescence, particularly regarding T cell subsets[217,218] and thymic atrophy.[217]

There is a well established link between viruses and senescence. Senescence can have major effects on susceptibility to viruses. Rendering human monocytic THP-1 cells senescent with galactose increases dengue infection, via increased production of IL-10 and the receptor for dengue, DC-SIGN.[219] Senescence induced by SARS-CoV-2 in lung tissue cells has been claimed to be a major driver of disease by increasing senescence-associated secretory phenotype driving inflammation; the senolytics navitoclax and dasitinib + quercitin eliminated senolytic cells in animal models with beneficial effects.[220] High levels of tissue senescence of lung cells with senescence-associated secretory phenotype were detected in the autopsies of COVID patients compared with non-SARS patients.[221] Viral infection may cause long-lasting immunosenescence with long-term effects.[222] In a genome-wide DNA methylation study 6 months after COVID-19 infection, there was evidence of epigenetic drift, with a significant acceleration of Horvath's epigenetic clock for aging.[223]

In terms of neurodegeneration, it has been reported[224] that senescence occurs in motor neurons of primates, as measured by senescence-associated β-galactosidase, produced by microglia—secondary to a 10-fold increase in chitotriosidase1 (CHIT-1) in CSF. CHIT-1 breaks down complex galactose chains (and transgalactosylates substrates). Levels of CHIT-1 in CSF are a biomarker for ALS progression.[225,226] Switching the energy source from glucose to galactose, in fibroblasts from patients with superoxide dismutase 1 (SOD1) mutations, reduced glycolysis and uncoupled the mitochondria, essentially creating an energy crisis,[227] which mimicked the same in ALS. Thus, it would appear to be important to study the breakdown of galactose-linked GSLs in viral infection and long COVID.

Immunosenescence occurs in long COVID[228] and has been postulated to be among the increased risks of the aging-associated changes in susceptibility to COVID-19 and long COVID.[229,230] In this respect, the RECOVER program has reviewed the incidence of long COVID with aging, indicating that there are different susceptibilities to aging, with differing spectra of symptoms, rendering comparisons difficult.[231] Aging is 1 of 6 steps involved in the initiation of ALS.[232] The links with aging and senescence, described above, may mean that there are very long-term effects of

severe viral infections, beyond those discussed in this review, which will need long-term follow-ups.

V. Glycosphingolipids and lipid metabolism in neurodegeneration: Similarity with pathways for viral infection

Glycosphingolipids have been shown to play critical roles in ALS,[129,233–239] in the pathogenesis of PD,[240–242] AD,[243–245] and lysosomal storage disorders.[246]

A. Key role for lipid metabolism and GM1 in amyotrophic lateral sclerosis

Lipid metabolism is markedly modified in ALS, particularly in research using the superoxide dismutase ($SOD1^{G86R}$) model. In this model, GBA2 (nonlysosomal glucosylceramidase; GCase) is increased 8-fold in spinal cord at the start of the decline in grip strength. Metabolomics and transcriptomic analysis in multiple tissues showed that ceramide/glucosylceramide ratio is critical also in human patients.[233,234,239] Ceramides are increased in muscle in ALS models.[234] GCS inhibitors exacerbate ALS models and increase denervation,[234,238] whereas GCase inhibitors are protective in ALS models, facilitating reinnervation in sciatic nerve crush, protecting neuromuscular junctions.[129,235] However, there were no major changes in sphingosine in these ALS models.[234,235] GM1 shows the structural complexity of glycosphingolipids and is a target for cholera toxin. Cholera toxin binding is markedly reduced in the presynaptic zones of neuromuscular junctions in $SOD1^{G86R}$ mice at the beginning of symptoms.[234] Presynaptic GM1, a component of almost all mammalian neurons, appears to be critical for maintaining the integrity of neuromuscular junctions (NMJs) and thereby prevents the metabolic changes involved in denervation.

The key changes in GSL metabolism in ALS are at the interface of ceramide/glucosylceramide (Fig. 1), which we[117,234,236,247] and others[233,238,239] have shown. In a transgenic mouse model (Cu/ZnSOD mutant mice), the spinal cord showed increased levels of sphingomyelin, ceramides, and cholesterol esters,[233] and these data are compatible with the observations of GBA2 being increased in the spinal cord, thereby increasing ceramides and depleting GSLs. Thus, GBA2 (and not lysosomal GBA1) was specifically increased 8-fold to 10-fold in the spinal cord of $SOD1^{G86R}$ mice and 75 and 105 days,[129] which would cause the breakdown of glucosylceramide and galatosylceramide,[131] potentially transglycosylating glucose to several sites. It will be therefore interesting to assess whether GBA2 is increased following viral infection.

However, there is a differential between long COVID and ALS patients regarding lactate metabolism, as ALS patients have low circulating lactate metabolism, even with the limited exercise they can perform,[248–250] and this is associated with disease progression.[249] In contrast, long COVID patients and ME/CFS patients have high circulating lactate for a given exercise workload compared with controls, due to mitochondrial dysfunction in skeletal muscle.[50,51] This may be explained by a significant difference between the 2 conditions, as models of ALS patients show preferential denervation of type II muscle, producing lactate, whereas this has not been reported to occur in long COVID, which is associated with inflammatory myopathy with mitochondrial engagement, following infection of muscle cells.[251]

Plasma and CSF NfL have been found to be a reliable measure of neurodegeneration and of cognitive decline following neurodegeneration.[252] Indeed, NfL levels in ALS have been taken as a surrogate marker for approval of Tofersen in ALS by the Federal Drugs Authority.[253] The results for NfL level elevation in long COVID have been mixed as NfL levels were either not elevated in reports of long COVID[15,254–256] or were, but in hospitalized patients[85,257–259] and associated with higher fatigue and cognitive impairment.[260] In a systematic review, only patients with neurological symptoms showed increased NfL levels.[261] NfL elevation was associated with severe infection but normalized after 6 months, although fatigue, brain fog, and cognitive changes were present.[262] Thus, these results do not indicate that long COVID harbors a severe underlying neurodegenerative process. Nevertheless, ALS and PD are multistep diseases, with aging taking 1 step[232]: could long COVID be another contributing factor?

B. Guillain-Barré disease

The first wave of hospitalized patients with COVID-19 was associated with 31 cases of GBS, but encephalopathies were more frequent.[263] Neurological manifestations were common in the first wave of COVID-19.[264] One case of COVID-19 was associated with reversible peroneal conduction block, with anti-GM1 immunoglobulin M positivity.[265] However, GBS was not more frequent after COVID-19 than in other respiratory infections,[29] but the risk was higher after hospitalization with COVID-19 compared with all other hospitalizations.[22]

C. Key roles for glycosphingolipids in Parkinson disease

Mutations in the GBA1 in Gaucher disease are causative of the pathology, and up to 30% of Gaucher patients have PD, associated with mutations in GBA1, which deleteriously affect enzymatic function in the lysosome, resulting in the massive increases in glucosylceramide seen in Gaucher disease. This is because GBA1 is a lysosomal enzyme, effective in acidic pH. Consequently, there are potential risks in inhibiting GBA1, as there are risks of inducing Gaucher disease or PD. Inactivation of GBA1 in oligodendrocytes causes lysosomal dysfunction, demyelination, and α-synuclein accumulation in mice.[266] Therefore, as GBA2 (the nonlysosomal glucosylceramidase) is increased in the spinal cord in the early stages of ALS and inhibition is beneficial, it is important that a compound modifying GCase acts as a chaperone at GBA1 and inhibits GBA2, while not inhibiting glucosylceramide synthase (*UGCG*). Inhibition of ceramide synthesis by myriocin increased transcription factor EB activation and increased autophagy and activates the transcription factor NRF2 while enhancing the expression of genes involved in dopaminergic neurotransmission.[267] Ambroxol also increases autophagy and metabolism associated with transcription factor EB, with an inverse relationship with α-synuclein in PD.[240] Ambroxol, inhibiting GBA2 with an IC50 of ~30 nM, can cause an increase in NMJs on spinal explants on myoblasts in tissue culture, having protective effects on denervation and grip strength in the $SOD1^{G86R}$ model of ALS and in denervation models (sciatic nerve crush).[129] The drug is a chaperone at GBA1, ameliorating lysosomal dysfunction, and favorably modifying α-synuclein levels.[240] Recent studies confirmed that the drug also inhibits acid sphingomyelinase,[268] which has previously been shown to be activated upon infection of epithelial cells with SARS-CoV-2,[269] which was inhibited by antidepressants and ambroxol.

Ledeen's group have emphasized that GM1 and GD1a is decreased in the brain and periphery of patients with PD[270–274] and that the administration of synthetic GM1 was beneficial in mice with disruption of GM3 synthase.[275] At least part of the protective effects of GM1 are proposed to be due to the mitigation of α-synuclein aggregation.[273] However, in contrast, it has been proposed that when α-synuclein binds to gangliosides in lipid

rafts, it switches to an α-helix form from random coil, forming Ca^{2+}-permeable pores leading to neurotoxicity.[132,276] However, although there are no direct studies linking the ganglioside binding of SARS-CoV-2 to that of α-synuclein, Fantini's group has designed a therapeutic peptide specifically targeting brain gangliosides, the adaptive peptide AmyP53. This peptide blocks the interaction of α-synuclein and Alzheimer β-amyloid protein with gangliosides and the formation of Ca^{2+}-permeable pores. By blocking the calcium-induced neurotoxic cascade, AmyP53 has been proposed for the prevention and treatment of AD and PD via direct targeting of brain gangliosides.[128,132,277]

VI. SARS-CoV-2 infection and the blood-brain barrier

It is therefore important to assess whether SARS-CoV-2 can access the brain. Extensive evidence indicates that SARS-CoV-2 infection causes cerebrovascular damage, which involves the blood-brain barrier (BBB). Indeed, cerebrovascular complications, including ischemic and hemorrhagic strokes, comprise a portion of post-COVID conditions.[278,279] There was a risk of intracranial hemorrhage of 0.6% at 6 months, and a risk of ischemic stroke of 2% in COVID-19 survivors within 6 months postinfection.[279] Part of these effects may be related to elevated thrombotic events that develop in these patients.[280] Interestingly, SARS-CoV-2 proteins have been observed to be associated with endothelial cells of small cerebral vessels in autopsy samples.[281] It has also been proposed that the injury to the BBB and the brain endothelium is associated with the risk of developing neuropsychiatric symptoms of COVID-19.[282] This notion has been supported by the reports of elevated albumin levels in the cerebral spinal fluid[283] and increased fibrinogen deposition in the brains of COVID-19 patients.[284] Extensive inflammatory changes involving the brain endothelium have been described in autopsy human samples with COVID-19.[284] Elevated levels biomarkers of vascular injury, such as soluble ICAM-1 or VCAM-1, and markers of BBB damage, such as S100β, are frequently found in plasma of COVID-19 patients.[282]

A recent study has been able to link sustained low-grade chronic inflammation (particularly S-100β, βFGF, GM-CSF, IL6, and TGF-β) and adhesion to brain endothelial cells by peripheral blood mononuclear cells to the occurrence of brain fog in long COVID. These changes were associated with volumetric changes in the brain, primarily associated with TGF-β.[285] This study also showed that reduced brain and white matter volume occurred in both patients with brain fog and recovered patients; hence, this was not the cause of brain fog, although it may lead to the possible changes in neurodegeneration. These authors also showed persistence of viral spike protein, which has been linked to long COVID symptoms. Spike protein has a long half-life in the body (localized in "nonclassical" CD16+ monocytes in patients with long COVID 15 months after infection[286]) and is associated with endothelial inflammation.

The involvement of the vascular system in SARS-CoV-2 infection raised possibility of direct infection of the vascular cells by the virus,[287] and several reports have correlated the infection outcome with vascular dysfunction.[288] It was indicated that the cells forming the neurovascular units of the BBB contain entry receptors for the virus, including ACE2, and the host protease transmembrane serine proteinase 2 (TMPRSS2).[289] In addition, endothelial cells contain the toll-like receptor 4, which was suggested to be involved in infection in an ACE2-independent mechanism.[290] Despite this favorable receptor profile, several reports failed to observe a productive SARS-CoV-2 replication in brain endothelial cells.[291–293] A productive infection has been observed in human-induced pluripotent stem cell–derived brain capillary endothelial-like cells (but not in more commonly used hCMEC/D3 cell line), however, only after employing a very high multiplicity of infection 10, which limits pathological relevance of these findings. Although not being productively infected, endothelial cells can be activated by exposure to SARS-CoV-2, which is reflected by the induction of inflammatory responses or mitochondrial dysfunction. Noncanonical NF-κB activation was proposed,[292] as the primary mechanism of SARS-CoV-2–stimulated activation of primary brain endothelial cells without viral replication in the endothelium. Moreover, inflammatory responses by endothelial cells, alterations of tight junction protein expression, and compromised barrier function were observed in response to treatment with spike 1 protein alone,[289,294] reinforcing the possibility that endothelial cells can be activated without the virus entering the cells. Thus, a long half-life of spike protein is potentially a major contributor to long COVID. In addition, stable fibrinoid micro-clots have been found in long COVID, which could compromise microcirculation in multiple tissues, causing, among other syndromes, postural orthostatic tachycardia syndrome.[295]

Although the consensus appears to indicate that brain endothelial cells are not a target for productive SARS-CoV-2 replication, evidence suggests that vascular pericytes may support productive infection.[296–298] Finally, it was suggested that SARS-CoV-2 can infect epithelial cells of the blood-CSF barrier rather than pericytes or endothelial cells.[293]

VII. Microglia, viruses, and metabolism

Neuroimaging using $PET^{11}C$ PBR28 showed widespread neuroinflammation in 12 long COVID individuals compared with 43 controls in multiple brain areas (midcingulate and anterior cingulate cortex, corpus callosum, thalamus, basal ganglia, and linings of the ventricles).[30] The effects, or presence, of viral infections in the brain are monitored by microglia via P2Y12 receptors, which are instrumental regulators of neuronal activity and fate, including the removal of terminally injured cells with marked impact on neurological outcomes.[299–301] Microglia have specialized metabolic junctions with neurons, with mitochondria linked to P2Y12 receptors (which sense adenosine 5′-triphosphate, and P2X7 receptors (sensing ATP release, which link to inflammasomes, produce IL1β, and inhibit Krebs cycle). Thus, microglia are critical for monitoring viral infections via P2Y12 receptors, which are instrumental regulators of neuronal activity and fate, including the removal of terminally injured cells with marked impact on neurological outcomes.[299,300,302] COVID-19 infection in mice increased sensitivity to the neurotoxin, MPTP.[303] The interplay of trophic and inflammatory effects on mitochondrial metabolism and neurodegeneration is a factor that plays a major role in neurodegeneration[210] and plays a major role in long COVID.

VIII. Status of incidence and progression of COVID-19 and long COVID on amyotrophic lateral sclerosis, Parkinson disease, and Alzheimer disease

A key question is whether COVID-19 infection leads to an increase in neurodegenerative disease incidence, severity, and rate of progression. GSLs are critical for the integrity of NMJs; indeed, the increase in GBA2 in the spinal cord of SOD1 mice at the beginning of symptoms[129] may explain why NMJs dismantle in ALS. In this respect, the conditions whose risk increased the most following 6 months of long COVID related to myoneural junction/muscle disease, in a study with more than a million participants in the UK.[29] However, these symptoms declined over 2 years, in a study of US veterans.[10]

A further complication is that SARS-CoV-2 may interact with the transactive response DNA-binding protein of 43 kDa (TDP-43), which is disrupted in almost all forms of ALS (reviewed by[304]).

The incidence of ALS was reviewed pre-COVID, showing increasing incidence and prevalence[305] but varying across the world with a range of incidences between 0.6 and 3.8 per 100,000 person years, with 2.1–3.8 in Europe. The prevalence ranged between 4.1 and 8.4/100,000 persons. However, during lockdown in 2020, ALS decline slightly accelerated (84 patients: monthly rate of amyotrophic lateral sclerosis functional rating scale-revised decline during lockdown) was 1.06 ± 1.42 and was significantly increased compared with the prelockdown period, 0.58 ± 0.73, corresponding to an 83% increase ($P = .007$).[306] Two patients were reported with much accelerated decline following infection,[307] and the death rate of US veterans with ALS was increased after 2019.[308] In a small sample, the death rate of hospitalized ALS patients with COVID-19 pneumonia was studied, but this may be due to lower healthcare access during confinement.[309] A small reduction in incidence in 2021 was found in an Italian study and attributed to delayed diagnosis.[310]

However, there has been no clinically relevant increase in ALS, but this must be surveilled in the future.

Infections and stress are well known to cause deterioration in PD disease, particularly atypical PD.[311] Thus, a large meta-analysis of 13,878 patients from 27 studies around the world found decreased physical activity and exercise, as to be expected, but with worsening PD symptoms (OR, 3.57, 95% CI, 0.96–13.34, $P = .058$), particularly in resource-limited countries.[312] However, patients with PD are older and hence at risk of COVID-19, without a particular molecular susceptibility. Furthermore, vaccination against SARS-CoV-2 may have been regarded as a potential threat to patients with PD. In this respect, of 9 cases of adverse effects postvaccination, 6 were of PD patients, and 3 of the development of movement disorders in healthy people, but all cases were resolved by appropriate therapy.[313]

A cohort study of 759 patients with PD in Italy[314] showed increased risk of major clinical outcomes following COVID infection, but the authors considered that this may have been due to less medical support and reduced exercise. Telemonitoring of exercise in patients with PD was only partially successful.[315]

IX. Bacterial and viral infection and Alzheimer disease

Systemic infection is an important contributor to dementia in AD,[316] as brain innate immune cells are primed rather than desensitized by infection,[317] and IL1β, elevated by infection, may impair cognitive function for over 2 months in patients with AD.[318] Viral infections have been associated with AD, although evidence is not conclusive, as yet, as to how causative they may be. Herpes simplex virus-1 and shingles (caused by varicella zoster virus and human herpes virus3) lead to an increased risk, offset by vaccination.[319–321] Furthermore, there is some molecular cross-talk between long COVID and AD.[322] An increased OR for AD was found post–COVID-19 infection (1.39), accentuated after hospitalization,[307] although this is hardly surprising because of the age-related susceptibility of both diseases, linked to loss of function (Fig. 6); hence, a severe infection could precipitate AD in elderly subjects who may have developed the disease 6 months to a year later. Analysis of UK Biobank confirmed a small risk of AD post-COVID infection, but an inverse or null association with ALS.[323]

Changes in brain gangliosides have long been known to be associated with AD,[324] and the central role of ceramides in the pathogenesis has been recently reviewed. There is an unresolved link with GM1 and AD. As GM1 and other gangliosides decline with age and in Alzheimer brain, presumably due to a loss of synapses,[325] Svennerholm perfused GM1 (20–30 mg/24 hours) into the lateral ventricles of 5 patients with AD for a year and reported substantial improvement.[326]

However, GM1 has been reported to cause amyloid-β fibrillogenesis in multiple studies, contributing to neurofibrillary tangles, reviewed by Guo,[107] which may imply "seeding" amyloid plaques. Both GM1 and GM3 colocalize with amyloid plaques,[245,327,328] and Enzlein et al[329] correlated plaque-associated GM1 with more aggressive pathogenesis, but it may also be associated with areas of greater synaptic disruption. However, the direct interaction of SARS-COV-2 with GSLs and gangliosides in the brains of subjects with mild cognitive impairment or AD has not been studied as yet, although mechanisms may be overlapping.

X. Pharmacological agents affecting glycosphingolipids

Although this article has shown the powerful interactions of viruses on GSLs, and on subsequent metabolic effects, modulators of glycosphingolipid metabolism have not yet been assessed in long COVID, hence, this section will be an overview of possibilities in the area.

A. Glucosylceramide synthesis inhibitors

Inhibition of synthesis of GlcCer has also been proposed as therapy using substrate reduction therapy drugs such as venglustat. However, GlcCer is the precursor of all complex GSLs, and hence, these drugs do not only reduce GlcCer levels but also gangliosides such as GM1, which are not only targets for enveloped viruses but also neuroprotective. There is therefore a possibility that brain-penetrant inhibitors of GCS might carry therapeutic risk. The brain-penetrant GCS inhibitor, GZ66716, was tested in 2 mouse models of synucleinopathy.[330] In the $Gba^{D409V/D409V}$ mouse model, GZ667161 reduced levels of glucosylceramide and glucosylsphingosine, while also reducing α-synuclein and tau accumulation. In a mouse model overexpressing synuclein (*A53T-SNCA)* the compound reduced α-synuclein accumulation and ameliorated cognitive deficits. Consequently, venglustat was developed for PD, but it was found that the drug was ineffective with a trend to deleterious effects, likely due to suppressing ganglioside levels downstream of GlcCer in the biosynthetic pathway,[331] although a complication in the pharmacology of GBA1 modulation has arisen in that *GBA1*, has a pseudogene *GBAP*1, with 96% homology in the coding region, which can lead to nonlysosomal directed products. Fortunately, for the GBA1 hypothesis, *GBA1* variants were still found to be the major genetic cause of PD, using long-read DNA sequencing.[332] However, GCS inhibitors may also be deleterious in denervation and ALS models.[235] Thus, although the inhibition of GCS may be beneficial, perhaps, in the build-up of lysosomal GSLs in monogenic lysosomal diseases, such as Gaucher disease with GBA1 mutations, they may be suboptimal in more complex polygenic neurodegenerative diseases.[234]

The iminosugar, miglustat, (*N*-butyl-1-deoxynojirimycin), inhibits GCS, with secondary effects on β-glucosidases, GBA1 and GBA2, and causes weak inhibition of SARS-CoV-2 replication in vitro.[333] Miglustat is marketed for type1 Gaucher disease and Pompe disease. The drug has some efficacy in reducing replication of hepatitis B virus and human immunodeficiency virus[334–336] and was also found to cause weak inhibition of SARS-CoV-2 replication in vitro.[333] In a screening of repurposed compounds, miglustat, lucerastat, and related iminosugars were found to have antiviral efficacy against SARS-CoV-2.[337] However, the potency against SARS-CoV-2 has been shown to act predominantly via glucosidase activity, whereas α-galactosidase and mannosidase inhibitors were inactive.[338]

B. Lysosomal β-glucosylceramidase chaperones and nonlysosomal β-glucosylceramidase inhibitors

GBA1 mutations are a major risk factor for PD, increasing risk by 5-fold to 6-fold[339] by inhibiting the breakdown of GSLs in the lysosome. Consequently, GBA1 chaperones, which bind to mutated GBA1 in the cytoplasm, and aid transport to the lysosome, where they may be released in the acidic pH, allowing enzyme activity, are an established therapeutic principle for both PD and Gaucher disease. A GBA1 chaperone, NCGC607, is an example, which is being developed for restoring GBA1 activity, reducing α-synuclein levels in induced human pluripotent stem cell–derived dopaminergic (DA) neurons from GBA-PD patients.[340]

The generic drug, ambroxol, has been reported to be a chaperone for GBA1, thereby increasing breakdown of lysosomal GSLs, reducing synuclein,[239,341] while inhibiting non-lysosomal GBA2,[129] increasing GM1 and also GM3. Ambroxol has beneficial effects in 2 ALS models (SOD1^{G86R}, TDP-43^{Q331K}, and CHMP2B^{intron5} mice).[129,247] Thus, the drug is in phase II for ALS (NCT05959850), starting phase III for PD (phase II complete NCT02941822,[342] phase II/III: NCT05287503, NCT06193421, NCT05778617, and NCT05830396), Lewy body dementia (NCT04588285), and type 1 Gaucher disease (NCT03950050). In a pilot study of neuronopathic Gaucher disease, high-dose (1300 mg/day) oral ambroxol had good safety and tolerability, passing the BBB, and decreasing glucosylsphingosine levels in CSF with recovery of motor function in 2 patients, allowing them to walk again.[343] The drug inhibits SARS-CoV-2 replication in vitro[344,345] but did not significantly change mortality in hospitalized patients with acute COVID.[346]

In contrast, the galactose analog, *N*-butyldeoxygalactonojirimycin (lucerastat) inhibited GBA2, rather than GBA1, with GBA2 activity being optimal at pH 5.5–6.0[347] but is primarily a GCS inhibitor, which was tested in Fabry disease but failed to meet its clinical endpoints.

From a crystal structure study, interaction energy for binding to GBA2 was: isofagomine >1-deoxynojirimycin > glucoimidazole > N-butyl-deoxynojirimycin ≈ N-nonyl-deoxynojirimycin > conduritol B-epoxide ≈ azepane.[348] Conduritol B-epoxide is 3-fold to 10-fold more potent on GBA1 compared to GBA2.[129] Selective GBA2 inhibitors are now in development as Alectos Therapeutics are developing ALO1811 with Biogen as an orally active agent for PD. Sinbaglustat inhibits both GCS and GBA2 and is in development with Idorsia for rare lysosomal disorders, effective in a *Glb1*$^{-/-}$ mouse model of GM1 gangliosidosis, lowering plasma levels of NfL, GlcCer, lactosylceramide, and complex GSLs, with more time being needed to lower the concentrations of the more complex GSLs.[349]

XI. Future risks for neurodegeneration, post–COVID-19

The text above indicates that GSLs may have major effects in both viral infections and neurodegeneration; thus, the key question is whether there is a major risk of COVID-19 or long COVID precipitating neurodegeneration. However, as most neurological disorders are age-dependent, this can lead to difficulties in interpretation of incidence, particularly as susceptibility to viral infection is age-dependent, and the COVID pandemic occurred so recently. For example, the incidence of ALS increases with age, but the global population is aging; hence, global ALS cases were postulated to increase from 222,801 in 2015 to 376,674 in 2040.[350] There are few publications on patient registries specifically looking at the incidence of neurological diseases post-2019, but our impression (and the impression of clinical investigator's that we have addressed) is that there is no major clinical increase of incidence in neurological disorders, except perhaps AD, since January 2020, which cannot be explained by poorer healthcare during lockdown. This also indicates that the incidence of neurological disorders in non-hospitalized patients in the US veteran's cohort is steadily declining 3 years postinfection.[13]

Although there are 551 studies listed in ClinicalTrials.gov, there are no approved drugs for long COVID, as yet.

XII. Nonpharmacological therapies: Exercise

As CMAH became a pseudogene (perhaps after viral infection), at the same time, as hominins increased metabolic capacity to run, the effects of exercise in long COVID are of interest. Exercise intolerance is a critical issue for many long COVID patients.[351] Some, but not all,[352] long COVID patients frequently have poor lactate clearance, associated with impaired lipid oxidation and exercise intolerance,[50,51] showing mitochondrial dysfunction. Peak VO_2 was highly significantly correlated with peak venous succinate and lactate and impaired systemic oxygen extraction.[353] In this respect, viral infection, with immediate effects on mitochondrial function, can be followed by long-term impact involving multiple mechanisms (hit and run,[354] as reported 12 years after SARS-CoV-1 infection.[87] Reviewing 46 exercise trials for recuperation following long COVID, the presence of postexertional malaise was a barrier to improvement, and the authors made a series of exercise recommendations for individualized therapies.[355] In a trial of 181 long COVID patients (PHOSP-COVID study), using a specific tailored exercise program based on fatigue, adapted to each patient, functionality and quality of life were partly restored.[356]

Patients with ALS lose strength rapidly, with a 44% decline in $VO_{2\ peak}$ and ~38% in peak power (watts) and lactate clearance in newly diagnosed patients <3 months,[250,356] associated with denervation and deconditioning, and degrees of mitochondrial dysfunction in skeletal muscle.[357] Individually defined low-impact training has recently reviewed and proposed to have beneficial effects in ALS.[358] Although there may be beneficial effects of exercise in ALS, restoration of function and quality of life has not yet been achieved.

Metabolomics has also been applied to patients with long COVID, with fatigue and exercise intolerance. Exercise intolerance was associated with higher blood lactate levels and lower fatty acid oxidation rates, with high acyl carnitine levels during graded exercise tests to volitional exertion, implying mitochondrial dysfunction.[50,51] In contrast, elite athletes have low blood lactate (until very high-power outputs) not only because they are using lactate as a power source but also because the low lactate allows lipid oxidation, which is the main energy source.[51,359] Thus, it is possible that mitochondrial dysfunction may be causative of lactate intolerance. Malonyl CoA limits lipid oxidation by inhibiting carnitine-palmitoyl transferase1, but high concentrations of lactate and pyruvate generate acetyl-CoA, lactyl-CoA, and malonyl CoA, inhibiting lipid oxidation, thereby facilitating glucose oxidation.[360,361]

SARS-CoV-2 is well known to have major effects on skeletal muscle, changing metabolism by involving sphingolipids,[362] and the spike protein has been shown to interact directly with lactate dehydrogenase B, promoting a switch from aerobic to anaerobic metabolism.[363] However, immobilization *per se* in healthy volunteers suppresses insulin-stimulated glucose disposal, following changes in pyruvate dehydrogenase kinase4, consequent to reduced muscle contraction. Confinement and sedentarism has been shown to reduce aerobic capacity, and neuromuscular junction damage.[364] Furthermore, confinement reduced access to healthcare, and patients with severe disease would take additional precautions not to be infected. Thus confinement, coupled with infection, may have long-lasting metabolic effects. At the opposite extreme, in Tour de France cyclists, GSL synthesis (GM3, GD1, and 3 hex-ceramides) and metabolism, and galactose metabolism were

second, third, and sixth ranked changes after race stages,[359] indicating the roles of GSLs in intense exercise.

Although tailored exercise may benefit some patients with long COVID, there is a spectrum of potential benefit, and patients with severe ME/CFS and postexertional malaise may be unable to exercise, and exercise may be deleterious due to localized ischemia.[365] Thus, propositions for personalized exercise therapies, but which are limited by the severity of postexertional malaise, seem the most appropriate.[351,355]

XIII. Conclusion

The critical paths of viral infection and neurodegeneration converge on GSL metabolism, and modification of GSL metabolism is, at last, the subject of much research. However, apart from the evident effects of severe viral infection precipitating incipient AD in the elderly, there does not appear to be an increase in neurodegenerative disease, despite the impact of long COVID on a very significant part of the world's population. It is interesting that viral infections have been modified by a major factor in human evolution (CMAH becoming a pseudogene~3 Mya), which probably allowed hominins to run, changing GSL and lipid metabolism. Hence, there is interest in modified exercise programs, when postexertional malaise is limited, in the therapy of long COVID. Thus, despite strong mechanistic links, current epidemiological evidence does not yet signal a dramatic surge in neurodegenerative diagnoses post-COVID. This may be due to the multistep nature of these diseases, the relatively short follow-up time, or the possibility that COVID-19 acts as an accelerant rather than a sole trigger. Continued surveillance is crucial, even if the present data are reassuring.

Abbreviations

ACE2, angiotensin-converting enzyme 2; AD, Alzheimer disease; ALS, amyotrophic lateral sclerosis; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CHIT-1, chitotriosidase1; CMAH, cytidine monophospho-N-acetylneuraminic acid hydroxylase; CSF, cerebrospinal fluid; CTB, cholera toxin B subunit; ER, endoplasmic reticulum; ER/G, endoplasmic reticulum/Golgi apparatus; GBA1, lysosomal β-glucosylceramidase; GBA2, non-lysosomal β-glucosylceramidase; GCS (or *UGCG*), ceramide glucosyltransferase; GlcCer, glucosyl ceramide; GSL, glycosphingolipid; IL1β, interleukin-1β; IRR, incidence rate ratio; Mya, million years ago; Neu5Ac, N-acetylneuraminic acid; Neu5Gc, N-glycolylneuraminic acid; NfL, neurofilament light chain; NGF, nerve growth factor; NMJ, neuromuscular junction; OR, odds ratio; PD, Parkinson disease; SOD1, superoxide dismutase 1; TDP-43, transactive response DNA-binding protein of 43 kDa; TMPRSS2, cellular transmembrane serine protease 2; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B.

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Conflict of interest

Michael Spedding is President of Spedding Research Solutions SAS, which is developing ambroxol for ALS and has a use patent and orphan drug designation for the indication. Bradley Turner is an organizer of the ambroxol trial. Jean-Philippe Loeffler and Alexandre Henriques are coinventors on the ambroxol use patent for ALS. Anthony Schapira is an organizer of a clinical trial of ambroxol in Parkinson disease. Frances M. Platt is an academic cofounder of IntraBio. Michael Zandi declares honoraria for one lecture each for each of the following mentioned in the last 4 years: Norwegian Neurological Society; Copenhagen Neuropsychological Society, Rigshospitalet, Cygnet Healthcare, GSK, and is an investigator on the UCL STIMULATE-ICP long COVID randomised controlled trial.

Data availability

The authors declare that all the data supporting the findings of the study are contained within the paper.

CRediT authorship contribution statement

Michael Spedding: Conceptualization, Writing – Original draft, Writing – Review and editing. **Johannes Aerts**: Writing – Review and editing. **Steve Alexander**: Writing – Review and editing. Aurelie-Gaelle **Bellozzi Woestelandt**: Investigation, Visualization. **Elena Chiricozzi**: Writing – Review and editing. **Alexandre Henriques**: Writing – Review and editing. **Pierre-Marie Lledo**: Writing – Review and editing. **Jean-Philippe Loeffler**: Writing – Review and editing. **Rushika Perera**: Writing – Original draft, Writing – Review and editing. **Frances M. Platt**: Writing – Original draft, Writing – Review and editing. **Pierre-François Pradat**: Writing – Original draft, Writing – Review and editing. **Frédérique René**: Writing – Review and editing. **Anthony Schapira**: Conceptualization. **Laura St Clair**: Writing – Original draft, Writing – Review and editing. **Kevin Talbot**: Writing – Original draft, Writing – Review and editing. **Maxime Taquet**: Data curation. **Michal Toborek**: Writing – Original draft. **Bradley Turner**: Writing – Review and editing. **Michael Zandi**: Writing – Original draft, Writing – Review and editing. **Pierre Gressens**: Funding acquisition, Writing – Review and editing.

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