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Fabry disease patients have an increased risk of stroke in the COVID-19 ERA. A hypothesis

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ABSTRACT

Stroke is a severe and frequent complication of Fabry disease (FD), affecting both males and females. Cerebrovascular complications are the end result of multiple and complex pathophysiology mechanisms involving endothelial dysfunction and activation, development of chronic inflammatory cascades leading to a prothrombotic state in addition to cardioembolic stroke due to cardiomyopathy and arrhythmias. The recent coronavirus disease 2019 outbreak share many overlapping deleterious pathogenic mechanisms with those of FD and therefore we analyze the available information regarding the pathophysiology mechanisms of both disorders and hypothesize that there is a markedly increased risk of ischemic and hemorrhagic cerebrovascular complications in Fabry patients suffering from concomitant SARS-CoV-2 infections.

Introduction

Fabry disease (FD) (MIM 301500) is an X-linked lysosomal storage disorder, characterized by decreased or absent activity of the lysosomal enzyme α-galactosidase A (α-GAL A) (EC:3.2.1.22). Stroke is a severe complication of this disease. The prevalence of cerebrovascular disease in FD patients identified in the *Fabry Outcome Survey* (FOS), was 11% in males and 15% in females, a prevalence 12 times higher than that observed in a comparable non-Fabry population [1]. In the global Fabry Registry, 6.9% of males and 4.3% of females with FD had an ischemic or hemorrhagic stroke. Furthermore, 50% of males and 38% of females suffered their stroke before the diagnosis of FD was made [2]. Moreover, FD has been identified as an under diagnosed etiology of stroke in the young [3–5] Among patients with FD and no history of stroke or transient ischemic attack (TIA), 44% of adults and 15.9% of adolescents had silent brain infarcts on brain magnetic resonance imaging (MRI) [6,7].

The recent coronavirus disease 2019 (COVID-19) is the third coronavirus outbreak in the past twenty years, preceded by the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS). The disease is caused by a member of the Coronaviridae family, defined as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and is considered the worst pandemic of modern times [8–10]. Stroke is emerging as a severe complication of the COVID-19 pandemic. It has been identified in 2.3% to 22% of patients with COVID infections and is associated with a ~ 2.5 fold increased disease severity [11]. Moreover stroke may be the first clinical manifestation of COVID-19 infection even in young patients lacking cardiovascular risk factors [12].

The pathophysiologic mechanisms of SARS-CoV-2 infection leading to stroke [13,14] overlap with those of FD [15,16] and therefore we hypothesize that there is an increased risk of stroke in patients with FD infected with Covid-19.

Stroke SARS-CoV-2 and Fabry disease

There are 4 different pathophysiology mechanisms enhancing the risk of stroke in COVID-19 patients that overlap with those of FD including: renin angiotensin aldosterone imbalance, vasculopathy, thromboinflammation and cardiac damage:

ACE2 Receptor Depletion and Renin Angiotensin Aldosterone Imbalance in COVID-19 infection [17,18]

In the renin-angiotensin-aldosterone (RAA) system, angiotensin (Ang) I is converted to Ang II by the angiotensin converting enzyme (ACE). Angiotensin II induces vasoconstriction as well as proinflammatory and pro-oxidative effects leading to endothelial dysfunction

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and activation as defined by the endothelial expression of cell-surface adhesion molecules, mediated by Ang II type 1 (AT1) receptor. ACE2 converts Ang II to Ang 1–7, which binds to both: Mas and MrgD receptors and induces opposite actions to the ACE/AngII/AT1 axis [19].

A dysregulated RAA system is considered an important mechanism in the vasculopathy induced by COVID-19 [17,20].

The coronaviral genome encodes four major structural proteins: the spike (S) protein, nucleocapsid (N) protein, membrane (M) protein, and the envelope (E) protein. The S protein is responsible for facilitating entry of the CoV into the target cell. The entry receptor utilized by SARS-CoV-2 is ACE2 [13,17]. ACE2 is a membrane-associated aminopeptidase expressed in vascular endothelia, renal and cardiovascular tissues, and epithelia of the lung, small intestine and testes. A region of the extracellular portion of ACE2 that includes the first α-helix interacts with the receptor binding domain of the SARS-CoV-2 S glycoprotein. SARS-CoV-1 and 2 viruses deplete ACE2 through receptor endocytosis upon viral entry, leaving ACE1 unopposed with generation of angiotensin II [14,17,18]. Angiotensin II not only worsens lung injury but also induces endothelial dysfunction and activation in organs like the heart and brain [9]. Similarly to COVID-19 infection an upregulated RAA system with enhanced AT1 activity has also been proposed as one of the main mechanisms for endothelial dysfunction and damage in FD leading to vasculopathy and stroke [16].

Vasculopathy: Endothelial dysfunction, activation and endothelitis

Endothelial dysfunction: Nitric oxide and reactive oxygen species (ROS)

Endothelial dysfunction is characterized by impaired endothelium-dependent vasodilation due to decreased nitric oxide (NO) bioavailability. Endothelial inflammation and oxidative stress are well established mechanisms leading to endothelial dysfunction [21,22].

ANG II through AT1 receptor stimulate the catalytic subunit of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, producing superoxide, H2O2 and loss of NO bioavailability. NO exerts a host of beneficial effects on the endothelium including regulation of cell survival and apoptosis, regulation of vascular tone and activation of antithrombogenic and anti-inflammatory pathways. NO can be rapidly sequestered by superoxide and converted into a long-lived, toxic reactive compound: peroxynitrite [17,18]. These mechanisms seem to be common to both Covid-19 infection and FD.

In FD there is evidence of increased ROS and deposition of 3-nitrotyrosine staining in dermal and cerebral blood vessels; a process that can be reverted by enzyme replacement [23]. Moreover, cortex homogenates exposed to GB3 showed an increase in the formation of reactive species [24]. Excess amounts of ROS may explain the increased resting regional cerebral blood flow identified in FD [25,26]. In addition mitochondrial dysfunction, further increasing ROS generation, occur in both: Covid-19 infected patients [19] and in FD [27].

Endothelial cell activation and endothelitis

Endothelial cell activation as defined by the endothelial expression of cell-surface adhesion molecules, including VCAM-1, ICAM-1, and E-selectin is induced by proinflammatory cytokines as seen in both: Covid-19 infected patients and FD (see below) and stimulates the recruitment and attachment of circulating leukocytes to the vessel wall [21]. Cell activation induces eNOS uncoupling, reduces NO synthesis and increases ROS production further enhancing endothelial activation. Moreover, NO benefits, that are lost, include inhibition of platelet reactivity and prevention of smooth muscle cell proliferation [21,28].

Expression of adhesion molecules in FD was analyzed both in endothelial cells and in leukocytes. A Fabry vascular endothelial cell line exposed to Gb3 overexpressed ICAM-1, VCAM-1 and E-selectin [29]. Moreover, an increased level of surface expression of CD11b and CD18 on monocytes [30] as well as CD31 in T cells, monocytes and granulocytes was observed [31] inducing leucocyte adhesion to the vessel wall and inflammatory infiltration of leucocytes into tissues [31–33]. Moreover in Covid-19 infected patients: postmortem studies confirmed viral endothelial inclusions and endothelial inflammation with evidence of endothelial and inflammatory cell death [34]. This damage is of particular relevance for patients with preexisting endothelial dysfunction including those with cardiovascular disease and risk factors including Fabry patients.

Inflammation and thrombosis

The activation of inflammation and a hypercoagulable state are common mechanisms in COVID-19 infected patients and FD. It has been postulated that SARS-CoV-2 inhibits type I IFN production facilitating viral replication and direct tissue damage. This stage is followed by the hallmark of COVID-19 infected patients: increased plasma concentrations of proinflammatory cytokines, including interleukin IL-6, IL-8, IL-10, IL-17, IL-18, IF gamma, TNF-α, monocyte chemoattractant protein 1 (MCP1) and macrophage inflammatory protein (MIP)1α [13,35–37].

The excessive and acute activated immune response seems to be due to pathogenic granulocyte–macrophage colony-stimulating factor (GM-CSF) + Th1 cells and inflammatory CD14 + CD16 + monocytes [37]. These activated cells are critical in neuro inflammation [38] and amplify the recruitment of immune mediators leading to hyperinflammation and a “cytokine storm“ [35–37]. Moreover, the lymphopenia, affecting patients with COVID-19, markedly reduces the immune modulating effect over the inflammatory process [35–38].

Accumulated glycolipids in FD, Gb3 and LysoGb3, are recognized as damage signals by toll like receptor 4 leading to overproduction of proinflammatory cytokines. Mononuclear cells, especially macrophages and dendritic cells from Fabry patients constitutively produce and secrete IL1bβ and TNFα and leukocytes infiltrate the tissues leading to fibrosis [39,40].

It is likely that the inflammatory mechanisms induced by the acute immune activation resulting from COVID-19 infection, might enhance and aggravate that of FD and vice versa damaging not only the lungs but also the heart, kidney and brain, the 3 most severely damaged organs in FD.

There is an association between systemic infection and stroke even in the absence of cardiovascular risk factors [41]. Bacterial or viral infections ~~may~~ increase the risk of cerebrovascular disease facilitating both: cardiac and arterio-arterial embolism [41,42].

A large number of viruses are associated with thrombotic complications in humans [43] SARS-COV-1 and SARS-COV-2 had also been associated with thrombotic events [13,44,45]. The stimulation of an inflammatory response is thought to be the predominant mechanism linking ischemic stroke with infection [46–48]. Inflammatory cascades promote plaque rupture, and thrombosis, leading to ischemic stroke. The enhanced inflammatory profile induces also a prothrombotic state mediated by attraction of macrophages, and white blood cells, activation of platelets and coagulation factors inhibition of fibrinolysis and complement deposition. The interaction between all these elements induces cloth formation in a process known as thromboinflammation or sepsis induced coagulopathy [14,17]. There is also a recognized association between viral infections and antiphospholipid antibodies production [49]. Antiphospholipid antibodies were reported both in COVID-19 [50] and FD patients [51] associated with both arterial and venous thrombotic events.

Hypercoagulability in COVID infected patients may even precede severe respiratory illness [52]. Autopsy findings have indicated thrombotic microangiopathy in multiple organs and mild thrombocytopenia high D-dimer and increased fibrinogen levels are associated with a more severe disease or death [53–58].

The end result of the infection induced systemic inflammatory response combined with endothelial dysfunction and microthrombosis is diffuse intravascular coagulation (DIC) [57,58]. In a recent study including 183 patients with COVID-19, 71% of COVID-19 patients who died fulfilled diagnostic criteria for DIC, compared with only 0.6%

among survivors [59].

Similarly patients with FD have a high risk of clinically relevant thromboembolic events including stroke, central retinal occlusion and recurrent thrombophlebitis [1,2,60–63].

There is a procoagulant and proinflammatory status in patients with FD manifested by endothelial cell activation, increased release of microparticles, activation of plasminogen, and, in some patients, elevation of D-dimer-products of fibrinogen breakdown [15,64,65]. In addition there is evidence of dysfunctional platelets favouring thrombosis and higher secretion of von Willebrand factor by endothelial cells in FD models [66].

Cardiac damage

Severe cardiac involvement is a relevant feature common to both disorders: Covid-19 infected patients and FD, predisposing to cardioembolic stroke or sudden death. The pathophysiology of cardiac injury due to SARS-COV-2 combines increased cardiac stress due to respiratory failure and hypoxemia, direct viral myocardial infections, the previously described systemic inflammatory response and a combination of all these mechanisms [67].

Cardiac involvement manifested by biomarkers elevations, is not only a frequent finding but also a feature associated with worse prognosis in COVID infected patients. ICU admission and mortality correlate with increased levels of troponin I and brain type natriuretic peptide [68–70]. Up to 17% of hospitalized COVID-19 patients suffered an acute myocardial injury manifested as acute myocarditis or damage secondary to hypoxemia [71]. Myocarditis is due to a combination of direct viral infection [72] and inflammatory cell infiltration [73] that leads to cardiac failure and sudden death [68,74].

Arrhythmia associated to SARS-CoV-2 including atrial fibrillation, conduction block, ventricular tachycardia, and ventricular fibrillation was observed in 7% of patients who did not require ICU admission and in 44% of patients who were admitted to ICU [75].

Cardiac involvement in FD is the main cause of death [76]. Hypertrophic cardiomyopathy is a hallmark of FD and evolves into a myocardial replacement fibrosis [77]. Lysosomal dysfunction triggers a cascade of events, including cellular death, inflammation, small vessel injury, oxidative stress, and tissue ischemia responsible for the cardiac damage [78–80].

The end diastolic volume of the left ventricle decreases with progression of the disease, diastolic filling is impaired, resulting in a reduction of stroke volume and cardiac output [78,80]. The conduction system is severely affected and implantable loop recordings identified asystole, bradycardia, intermittent atrial fibrillation and episodes of ventricular tachycardia; all of which markedly increase the risk of sudden death and cardioembolic stroke [81].

In summary based on the described pathophysiology mechanisms we hypothesize that the combined effects of increased Ang II, vasculopathy, thrombo inflammation and cardiac damage in Covid-19 infected patients which overlap with similar mechanisms in FD markedly increase the later patients risk of stroke even in the absence of respiratory symptoms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflicts of interest

Dr Reisin, Dra Rozenfeld and Dr Bonardo do not have conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110282.

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