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Research Article

Impact of COVID-19 Infection on Induction of IgA Antiphospholipid Antibodies:Thrombo-Inflammatory Risks to Pregnant Women

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Abstract

Infection caused by SARS-CoV-2 has been shown to induce the production of IgA antiphospholipid antibodies most likely secondary to activation of the respiratory mucosal immune system. These IgA antiphospholipid antibodies have been linked to thromboembolic events in hospitalized COVID-19 infected patients. Systemic changes in pregnancy, such as increased production of coagulation factors and decreased protein S anticoagulation activity, result in a 5-fold increase in thromboembolic events compared to non-pregnant women. Clinicians who care for hospitalized pregnant women infected with COVID-19 should initiate appropriate thromboembolism prophylaxis.

Keywords

Covid-19; Iga Antiphospholipid Antibodies; Thromboembolism; Immunity

Corona Virus (COVID-19)

The December 2019 a novel Coronavirus was discovered in Wuhan, China and continues to be a serious threat to public health. In February 2020 the World health organization (WHO) designated this disease COVID-19, short for coronavirus disease 2019 and declared it a pandemic on March 12th, 2020 [1]. Most of our understanding of this virus during this pandemic is derived from research built on recent experience and via analogies drawn from knowledge based on other known coronavirus serotypes.Despite the growing fund of knowledge about the etiology, transmission mode, diagnosis and management of COVID-19, much remains unknown and subject to speculations and anxious concerns.

COVID-19 Induction of the Immune System

One evolving concern is the effect of COVID-19 on the immune system, and the subsequent production of IgA antiphospholipid antibodies (APA) [2]. These IgA antibodies, produced in response to inflammation of the mucosal immune system, and the lupus anticoagulant (LAC) have been linked to thromboembolic events in hospitalized patients [2, 3].This is of particular interest with new autopsy studies emphasizing the hypercoagulable and inflammatory state detected in tissues from patients who die from COVID-19 infection [4]. In the previous decade, the severe acute respiratory syndrome-associated coronavirus (SARS-CoV-2) was also linked to venous thromboembolism in multiple organ systems [5]. With the realization that many deaths associated with Covid-19 have been related to thromboembolic events, a consensus statement recommends anticoagulation in many hospitalized Covid-19 patients [6].Evolving evidence implicates the three pillars of Virchow's triadin the pathogenesis of thromboembolism: namely endothelial damage, stasis, and hypercoagulability [7, 8]. Simultaneously, data links aberrant hemostasis to inflammation during viral infections [9, 10]. With growing interest in the "thrombo-inflammatory" aspect of COVID-19 infection [11] much remains to complete the picture, highlighting the possible role of APA and LAC in the process.

Association of IgA Antiphospholipid Antibodies with Thrombosis

IgG and IgM APA is associated with thrombosis in humans [12]. In clinical practice, IgA antiphospholipid antibodies are usually transient and related to inflammation. Recently, a study of 57 patients with isolated IgA antiphospholipid antibodies found that over 50% had thromboembolic clinical complications including venous and arterial thrombosis [13]. Moreover, animal models have indicated a strong association with thromboembolic events [13]. Although IgA APA are not considered as a part of the diagnostic criteriafor antiphospholipid syndrome, most clinical laboratories in the US test for IgA anticardiolipin antibodies, IgA anti phosphatidylserine antibodies, and IgA anti beta 2 glycoprotein antibodies [14].

Mechanism of Covid-19 Activation of Antiphospholipid Antibodies

The initial step in unravelling possible effects of COVID-19 on immune related thromboembolism in infected individuals lies in understanding the virus. The underlying culprit of COVID-19 is RNA virusSARS-CoV-2, previously referred to as 2019-CoV. This virus is one of 6 other strains of human coronaviruses. Other coronavirus infections include the common cold (HCoV 229E, NL63, HKU1, OC43), Middle East Respiratory Syndrome (MERS-CoV) and Severe Respiratory Syndrome (SARS-CoV-2) [15]. Full genome sequencing and phylogenetic analysis showed that SARS-CoV-2 or the coronavirus causing COVID-19 is a beta-coronavirus similar to SARS and MERS virus.

The virus has been shown to utilize the same angiotensin-converting enzyme 2 (ACE2) receptor and cellular serine protease TMPRSS2 for cell entry as the SARS virus [16]. Covid-19 uses the ACE2 receptor found in the lower respiratory system leading to an inflammatory response with activation of cytokines and chemokines resulting in respiratory distress and multi-organ failure [17]. Contrary to thrombotic events in other circumstances such as malignancy, the prominent inflammation-mediated component resulting from the presence of the virus and its products could trigger the "thrombo-inflammatory' cascade [2, 9]. A recent case of new-onset systemic lupus erythematosus associated with Covid-19 and APA was associated with a deregulation of the cytokine response resulting in multiple deep venous thromboses [18].

Pregnancy is an Acquired Hypercoagulable State

Systemic changes in pregnancy result in 5-fold increase in the risk for venous thromboembolism compared to non-pregnant women of the same age [19]. These changes include increased placental production of thrombin, platelet activation, blunting of fibrinolysis by plasminogen activator inhibitor type 2, vascular stasis in the legs and gravid uterus, decreased protein S anticoagulant activity, increased activated protein C resistance, and increased production of factor II, VII, VIII, X, and XII [20]. The net result is increased clot formation, extension, and stabilization. Antiphospholipid antibodies are an additional acquired hypercoagulable state and, when found in combination with clinical conditions such as recurrent pregnancy loss, result in the recommendation for anticoagulation during pregnancy [12, 19].

Placental Thrombosis after Covid-19 Infection

Evidence available on SARS-CoV-2 infection showed multiple organ involvement beyond the respiratory system including the immune, gastrointestinal, neurological, renal, circulatory, and genitourinary system [21]. In a study conducted in 2010, pathological changes to the systemic vasculature and circulation after SARS-CoV-2were found to result in thrombi in the lungs, spleen, pancreas, kidneys, adrenal glands, and mesenteric lymph nodes [5]. Symptoms of COVID-19 infected individuals depend on involved organs, which seem to parallel ACE2 receptor distribution [22].The ACE2 receptor has been identified in placentas between 14 and 40 weeks of gestation [23]. Recently placentas from five full-term births to COVID-19 patients were found to have histology indicating problems with fetal vascular perfusion with focal avascular villi and thrombi in larger fetal vessels [24].

Prophylaxis in Hospitalized Pregnant Women Infected with Covid-19

Evidence regarding COVID-9 infection in pregnant women is increasing. Most articles focus on severity compared to infection of non-pregnant women, obstetrical morbidity, neonatal morbidity, and possibility of vertical transmission. Pregnant women should practice social distancing, hand hygiene, and other recommendations for limiting exposure to COVID-19. Increasing reports of thrombosis in hospitalized patients suggest a systemic effect, such as antiphospholipid antibodies, and/or a direct inflammation of the vascular endothelium [6, 25]. Recently, The American Society of Hematology, the Society of Critical Care Medicine, and the International Society of Thrombosis and Hemostasis recommended venous thromboembolism prophylaxis in all hospitalized patients with COVID-19 including antepartum and postpartum women [26]. The recommendation included the use of unfractionated heparin in women close to delivery and low-molecular heparin in those remote from delivery or post-partum

Conclusion –Need for Additional Research

Despite the growing fund of Covid-19 knowledge, little evidence is available regarding the induction of the immune system via respiratory infection, production of IgA antiphospholipid antibodies, and the development of a systemic immune response. These data are critical particularly given the fact that a large proportion of COVID-19 patients fall victim to thromboembolic events subsequent to the initial respiratory distress [6, 25]. The expected implications of such findings are countless including offering better counselling, enhancing best practice management and designing therapeutic strategies in clinical practice targeting COVID-19 patients to overcome a vicious thrombo-inflammatory component of the SARS-CoV-2 infection [27, 28].

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