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The ABC's (Autoimmunity, Blood Type, Cytokines) in Types and Severity of Reactions to COVID-19 Vaccines.

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ABSTRACT

Based on initial reports of the association of blood types, especially type A, on increasing susceptibility and more severe disease in patients with Covid-19 disease, an observational study was performed to determine if there would be any correlation of bad side effects to the COVID-19 vaccines, associated with blood types, especially type A. At the time of study, only mRNA vaccines had been approved and available, thus Moderna and Pfizer were the ones evaluated. If an association was found, then the same evaluation could be done with vector vaccines, such as Johnson and Johnson, which was recently approved. Vaccine reactions were categorized as "Bad", if the participant experienced 6 of 9 of the following symptoms: fever (temperature ≥100.4 F), extreme fatigue, headaches, body aches, chills, nausea, vomiting, arm soreness > 3 days, and numbness in any area of the body. "Moderate", having 3 or 4 of the symptoms and "Mild", having 1 or 2 symptoms. Comparing participants with bad reactions; 28 of 39 type A (71.7%) vs. 4 of 39 type O (10.2%) experienced bad reactions, (Chi-square found P<.001). When comparing participants with at least moderate reactions, type A, B, AB together (52) vs. type O (39), there were 40/52 (76.9%) in type A, B & AB group, vs. 7/39 (17.9%) in type O people. There have been reported findings of patients with prolonged, long term and chronic health consequences, months after the initial illness, referred to as (Long COVID). If these are seen as a result of vaccination too, especially those with severe initial reactions, people may find themselves deciding if the risk of developing a chronic illness, outweighs the risk of acquiring the COVID-19 disease.

***Abbreviations:** Coronavirus disease (COVID-19); World Health Organization (WHO); Center for Disease Control (CDC); Acute Respiratory Syndrome (ARS); Electric Health Record (EHR); Emergency Use Authorization (EUA); Interleukins (IL).*

Keywords

COVID-19, ABO Blood type, Cytokines, Autoimmunity, Cytokines, Sars-CoV2, Coronavirus.

Introduction

In March 2020, The World Health Organization (WHO) declared a world pandemic due to Sars-CoV-2, commonly referred to as COVID-19 [1]. The virus was first identified in Wuhan China in late November of 2019 and was declared a Public Health Emergency of International Concern in February of 2020. One month later, a pandemic was declared [2-4].

As of March 22nd, 2021 there have been 123 million confirmed cases, with 2.7 million deaths, making some believe that in will be considered as one of the deadliest global pandemics in history, along with the Spanish Flu in 1918-1919 and the "Black Death" outbreak of bubonic plague, in the 1300's with estimated 75-200 million deaths [2,6-8].

The global social, economic and psychological effects have been devastating [9-13]. Companies closed, jobs were lost, and children's education was now the responsibility of parents who already were struggling to provide sufficient food to feed the

family [14-17]. Lockdowns, quarantines, isolation, contract tracing, and mask wearing were words heard daily. Weddings, proms, graduations and holiday family gatherings were cancelled. The only way to "see" (consult) a doctor was by telemedicine, not an option for many older people without computer skills, or people with economic hardships that could not afford, or have access to a computer. Life was put on hold, as were the funerals for the thousands that were dying daily [18-38].

There was an urgent need to find ways to test for the virus, treat it, and prevent the quick down spiral, resulting in hospitalizations, intubations, and in some cases, death, due to Acute Respiratory Syndrome (ARS). Would there be answers as to why one person was more susceptible to getting the virus, than another? Why do some family members living together get the virus but experience vastly different courses of disease, from mild cold like symptoms, or more serious flu like symptoms, whereas others end up hospitalized, and in some cases die?

Asymptomatic carriers were one of the biggest concerns, unknowingly spreading the virus at alarming rates [39-43]. Most importantly, there was the need to quickly develop a vaccine to prevent the rapid spread of it. Thirteen pharmaceutical and biotech companies were racing to be the first to develop and bring to market, the solutions to these problems [44].

Pfizer and Moderna quickly became the front-runners in developing a vaccine, both using mRNA, which had never before been approved for use. Pfizer crossed the line first, receiving Emergency Use Authorization (EUA), in the United States (U.S.), on December 11th, 2020. Moderna soon followed with their EUA one week later [45-48]. A process of development, to market, that normally takes 8-10 years, was accomplished in 10 months. There were also viral vector vaccines in development. Johnson & Johnson had their vaccine receive U.S. EUA in March 2021. AstraZeneca's vaccine, also a viral vector, is being used in several countries, but a few have opted to halt rollouts after reports of blood clots in some vaccinated people [49]. It has not yet received approval in the U.S., but is currently under FDA review.

There was also skepticism regarding the general safety profile of the mRNA vaccines, due to how quickly they were developed and marketed (one tenth of the time), as prior ones. Did the trials include participant's representative of ethnicity, gender, race, age and co-morbidities, such as diabetes, cardiac disease, obesity, or concurrent autoimmune disorders? Would these vaccines calm the concerns of hundreds of millions of the world population and allow life to get back to "normal"?

A few different theories have been explored to answer the question of why some individuals are more susceptible to get the COVID-19 virus, and develop severe illness if they do.

Autoimmunity

Autoantibodies, a hallmark of autoimmune disorders, have also been detected in Covid-19 patients. It is thought that the virus can trigger an autoimmune response through cross-reactivity with host cells [50]. A recent finding from NIH found that 10% of severe disease cases had misguided autoantibodies that attack the immune system, rather than the virus, leaving the body without a key defense against the virus. An additional 3.5% carried a genetic mutation that inhibits an effective immune response [51]. Having an autoimmune disorder increases vulnerability to serious illness, complications, and possibly death. Even a mild case can cause an exacerbation of a preexisting autoimmune condition [52-54]. While most viruses find ways to evade the body's defenses, research is finding that this coronavirus unhinges the immune system in a more profound way [55].

Blood Type

The thought that blood type can be linked to susceptibility to certain illnesses came about decades ago. In the 1970's, cholera was reported to be more frequent in individuals with "O" blood type and in 1993 people with type "O", were reported to be more likely to have Helicobacter pylori, due to more gastric mucosa receptors. The first report of possible link of blood type and Corona virus was the SARS-CoV, in 2002. In 2020, scientists in Wuhan China, in a non-peer reviewed article, reported that in a group of 2173 patients, type "A" patients had a higher risk of COVID-19 and patients with type "O" had a lower risk [56]. Since then, there have been numerous studies on associations of severity of disease and blood types. Some reported people with type A blood have an increased susceptibility, and increased risk of complications, if they become ill with it. However, other studies reported increased susceptibility of getting virus with type a blood, but decreased risk of complications and others have reported finding no correlation with blood type and susceptibility, or severity, of disease [57-64].

Another recent finding is that the antibody protects against getting the virus, or subsequently developing serious illness from it. Thus, people with types B&O blood are better protected (have the A antibody) then types A and AB (do not have A antibody) [65]. A recent finding in the March 3rd issue of *Blood Adv,* the authors reported that in lab experiments, the receptor binding domain of the coronavirus, that binds to cells to jumpstart infection, are associated with type A antigens, especially on cells that line the respiratory tract of the lungs of people with blood type A [66].

Cytokine Storm

Another concept for the varying range of disease severity, and effects progression to hospitalization, is due to the increased formations of cytokines and chemokines. This can result in acute injury to lungs [67].

Cytokines are proteins are communicators that signal the body to mount an immune response and are an essential part of the body's inflammatory response. However, if there is an over aggressive response, the amount of pro-inflammatory cytokines, such as interleukins (IL)-2, IL7, IL10, interferons, and tumor necrosis factor (TNF), they can increase rapidly, causing activation and delivery of macrophages, neutrophils and T cells to the site of infection, with destructive effects. This is referred to as a "Cytokine

Storm". The lung is often the area where this happens, and it can result in acute injury, leading to acute respiratory disease (ARD) and possible death. It can also occur in other organs of the body [68-71].

Again, one of the questions about cytokine storm, is what makes someone more susceptible to developing it? Is it due to genetics, or does the virus cause such an aggressive immune response, that the magnitude of cytokine release in overwhelming [72]?

Based on previous reported studies suggesting that people with type "A" blood may have more severe symptomatic and worsening disease outcomes, we did an observational study to determine if blood types had a similar effect on reaction types, and severity, after receiving the second dose of a mRNA COVID-19 vaccine.

Materials and Methods

This observational study included 91 people, ages 18-90, who knew their blood type and had received their second dose of either the Moderna, or Pfizer Covid-19 vaccine. Each was asked the following questions:

1) Did you have any reaction after the second dose of vaccine?
   a. If yes: What was the reaction(s) and how bad and how long it lasted?
   b. Which vaccine did you get?

Since the answers to the questions were subjective, and "bad" to one person may be mild to another, we developed a grading system to categorize the reactions of the 9 most frequent reported reactions (symptoms); fever (temperature >100.4 F), extreme fatigue, headaches, body aches, chills, nausea, vomiting, arm soreness > 3 days, and numbness in any area of the body. The reactions were categorized as:

Bad (severe): having 6 of the 9 symptoms.

Moderate: having 3-5 of the symptoms.

Mild: having 1-2 of the symptoms.

Slight: sore arm only for < 3 days.

Results

Of the 91 people who participated, the distributions of blood types were similar with that of the general population of the United States: Type A: 39/91 (42.8%), Type B: 9/91 (10%), Type AB: 4/91 (4.4%), Type O: 39/91 (42.8%).

The percentage of types of reaction according to blood type is seen in Table 1. For bad (severe) reactions, comparing type A vs. type O (the two largest groups), a bad reaction was found in 71.7% (28/39) of type A vs. 10.2% (4/39) of type O (p<.001). Though the numbers are too small to be of value, it was found that 2/4 (50%) participants with AB had a severe reaction and 1/9 (11.1%) with type B. Only 3 of 39 (7.6%) type A participants had no reaction, or a sore arm only vs. 26 of 39 (74.1%) with type O, as seen in Table 1.

Table 1: Results reactions per blood type.

Blood type of 91 people	Bad[a]	Moderate[b]	Mild[c]	Slight/none[d]
Type A #39 % 42.8	28 (71.8%)	5 (12.8%)	3 (7.6%)	3 (7.6%)
Type B # 9 % 10	1 (11.1%)	4 (44.4%)	3 (33.3%)	1 (11.1%)
Type AB # 4 % 4.4	2 (50%)	0	0	2 (50%)
Type O # 39 % 42.8	4 (10.2%)	3 (7.6%)	3 (7.6%)	29 (74.1%)

Reactions/Symptoms: fever (temperature >100.4 F), extreme fatigue, headaches, body aches, chills, nausea, vomiting, arm soreness > 3 days, and numbness in any area of the body.

[a]: 6-9; [b]: 3-5; [c]: 1-2; [d]: sore arm for < 3 days

The results are consistent with previous reported findings, by various groups, that people with type O blood were less likely to suffer severe illness and complications when having Covid-19 virus. When comparing types A, B, AB together vs. type O, with at least moderate reactions, were reported in 40/52 (76.9%) and 7/39 (17.9%) respectively.

Evaluating for bad reactions in participants with A antigen, thus no A antibody (A & AB types), vs. participants with no an antigen, thus having an antibody (B & O types), significant differences were seen; 30/43 (69.7%) vs.5/48 (10.4). (p<.001).

Discussion

The World Health Organization estimates that 10% of the world population of 7,874,965,825 has been infected with COVID-19. That translates to 787,000,000 people. Currently, as of March 2020, there were 123,000 confirmed cases, with 2,700,000 deaths [2]. That leaves 679 million unconfirmed cases and possibly up to 5% of them dying. Testing and isolating to prevent spreading are long in the past. Shortages and lack of equal distribution for test kits were a problem from day one of the pandemic. The way to control the spread appears to be thru vaccinating. Numbers are starting to plateau in countries where vaccines are available, but hundreds of million more doses are needed, as is education on the importance of being vaccinated, and calming the fears of the public of receiving it [73-77]. A world that in the last century, exploded in science and technology, from developing drugs for cancer and disease, to putting men and women on the moon, satellites in space, and computer technology beyond the imagination, is being brought to their knees, similarly to 1918 spanish flu pandemic, by a virus. The risk of grandchildren and their grandchildren never knowing the emotion evoked by a smile on a teacher's face, by a friend's hug, or the feeling of accomplishment at their graduation, is unthinkable. Will days of no masking be as foreign to them, as a rotary phone is to anyone under the age of 60? The number of cases seem to be slowing, but so is the availability of doses of vaccine. As new ones are being developed, unfortunately, so are

other strains of the virus. The need to develop and manufacture quickly, but safely, is of utmost importance.

Although there are many reports of ABO blood types and susceptibility and severity of the actual COVID-19 disease, a recent internet search did not find any studies on correlation of blood types and vaccine reactions. Thus, inference was drawn from data on the correlation of blood types with Covid-19 illness. The observational study presented here interestingly shows an association with A blood type and more severe reactions, after the 2nd dose of vaccine. There seems to be a correlation of blood type on the response to what the body considers foreign, similar to previous reported findings of increased severity of illness in COVID-19 patient, especially ones with type a blood [57-63].

These results also seem to correlate with the findings of Hoiland et al, regarding that A antibody provides some protective effect in severity of disease, similar to our study showed a greater number of participants without the A antibody experienced severe reactions to the vaccine, compared to those who had A antibodies [65].

There have been findings that there is no correlation of blood type and COVID-19 severity. A meta-analysis of nine observational studies with pooled data from 233,000 patients, showed no significant differences in severity outcomes of COVID-19 illnesses in A/AB vs. B/O blood types. However, when they looked an Italian and Spanish subset, there was an increased risk for severe illness, defined as respiratory failure, but no mechanical ventilation needed, in the A and AB blood types [58]. Ramo et al., presented at the ASH Annual Meeting (virtual) that in a study of 1,488 patients there was no association in disease severity, mechanical ventilation, or mortality between blood types [78].

Although our study showed significant differences in type A vs. type O people, in severe reactions, it was a small study that did not correct for other factors, such as age, race, ethnicity, gender, or co-morbidities, such as obesity, cardiovascular, diabetes, and other known related comorbidities. Perhaps these findings will lead to larger studies, since it does provide correlation with some previous findings of blood type in COVID illness.

There are other possible causes of susceptibility and complicating severity of COVID-19. Cytokine storm is considered to be the main factor that occurs, in a minority of patients, leading to serious complications, such as ARD, in the lungs, and possible death. It can also cause persistent damage to other organs in the body [67,68]. An overly aggressive response of proinflammatory cytokines, such as interleukins, interferons and TNF, can trigger an uncontrolled immune response and activate macrophages and lymphocytes that infiltrate cells, due to an increase permeability response to allow infiltration. If the inflammation from this is too severe, fibrosis may occur, which further damages the involved organs. Thus, at a certain point it is necessary for the body to stop the increased tissue permeability. In the extreme, excessive permeability may lead to immune paralysis, which starts the cascade of cytokine storm and subsequent death.

Infection with COVID-19 can also cause severe symptoms due to the immune defenses of some people. They may not be capable of limiting viral spread early in the infectious process, or the hyperactivity of the immune system. Some may have a genetic or autoimmune predisposition, making them more susceptible to an excessive cellular permeability problem, leading to increased absorption of irritants into tissues, causing an over activation of immune response. For example, this may be related to its binding to host cells utilizing the angiotensin converting enzyme II (ACE2) [79,80]. There could also be a genetic linkage for blood type to effect severity of SAR-2 virus, related to this increase permeability. We have previously reported an increased risk of excessive, inflammatory response from this excessive cellular permeability disorder, in a variety of chronic illnesses, that seems to respond to drugs releasing more dopamine, such as dextroamphetamine sulfate, which, in turn, may decrease the excessive permeability [81-83].

Should it be confirmed that people with type A blood are likely to have more severe reactions to the COVID-19 mRNA vaccines than other blood types, additional studies using viral vector vaccines might be considered, to determine if reactions were possibly due to the mechanism of action of the mRNA vaccine. Furthermore, it is known that some individuals who acquire the COVID-19 virus may have persistent symptoms lasting months and have an increase the risk of developing "autoimmune" symptoms, known as Long COVID [84-87]. It remains to be seen if some individuals will develop similar long-term affects following the vaccines, as have been reported in people with the actual COVID disease.

It would be also be interesting to determine if people who develop Long COVID-19 from the actual infection, or from the vaccines, will respond to sympathomimetic amines, or other drugs releasing dopamine, similar to the patients with chronic ailments that respond so well to this therapy. If so, this could suggest that other viruses, or pathogens, could play a role in the development of these autoimmune conditions.

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