



Interleukin Deficiency Disorder Patient Responses to COVID-19 Infections

Bruce S. Gillis^{1*}, Igor M. Gavin¹, Farnaz Barkhordar¹, Gayatry Mohapatra², Ming Jin² and Frederick G. Behm²

¹*Epic Genetics, 11801 W. Olympic Blvd, Los Angeles, California, USA.*

²*University of Illinois College of Medicine at Chicago, USA.*

Authors' contributions

This work was carried out in collaboration among all authors. Author BSG designed the study, analyzed the data with the assistance of the other authors and wrote the manuscript with the assistance of the other authors; author IG performed data analysis and analyzed patient specimens as did authors FB, GM, MJ and FB designed the study, analyzed patient specimens and assisted in the preparation of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2021/v33i830884

Editor(s):

(1) Dr. Syed Faisal Zaidi , King Saud bin Abdulaziz University for Health Sciences, Kingdom of Saudi Arabia.

(2) Dr. Rameshwari Thakur, Muzaffarnagar Medical College, India.

(3) Dr. Kalpy Julien Coulibaly, Félix Houphouët-Boigny University, Côte d'Ivoire.

(4) Dr. Masahiro Hasegawa, Mie University Graduate School of Medicine, Japan.

Reviewers:

(1) Mirel Alberto Feria Martínez, Universidad Tecnológica de La Habana José Antonio Echeverría (Cujae), Cuba.

(2) Sergio Felipe Dávila Cabrera , University of Havana, Cuba.

(3) José Hiago Feitosa De Matos, Universidade Regional do Cariri, Brazil.

(4) Lim Ming Chiang, Hospital Sultan Haji Ahmad Shah, Malaysia.

(5) Raíssa Maria Alves Soares Costa, Pitágoras College, Brazil.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/66972>

Original Research Article

Received 12 March 2021

Accepted 02 April 2021

Published 07 April 2021

ABSTRACT

Background: The chemokine, cytokine interleukin deficiency disorder defines the immune deficiency disease of fibromyalgia and a reduced ability to produce IL-6 and IL-8. Recent research has demonstrated improved outcomes in COVID-19 infections treated with IL-6 antagonists.⁹ These fibromyalgia cytokine deficient patients were screened for COVID-19 infections and associated morbidity and mortality rates.

Methods: Two cohorts of FM/a test positive fibromyalgia patients were evaluated. Initially, 4,631 patients were screened to determine the occurrence of known COVID-19 infections. Subsequently, 2,195 FM/a test positive patients underwent COVID-19 antibody testing.

Results: A total of 7,375 fibromyalgia patients were screened for the occurrence of COVID-19 infections. Of these, 4,631 individuals responded to an email-based inquiry to determine the occurrence of documented COVID-19 infections. Only 10 reported having symptoms consistent with and were diagnosed with COVID-19 by a healthcare professional, making for an incidence of .22%. Another 2,195 fibromyalgia patients completed health questionnaires and COVID-19 antibody testing and 82 had evidence of COVID-19 antibodies with 42 exhibiting symptoms and confirmed diagnoses. Of the remaining, 23 were asymptomatic. There were no deaths and only 1 hospitalization in this group.

Conclusion: Individuals with FM/a test positive fibromyalgia have a reduced ability to produce IL-6 and IL-8 which play significant roles in the cytokine storm complications associated with COVID-19 infections. When screened for evidence of past COVID-19 infections, these patients experienced an extremely low incidence of COVID-19 infections based upon antibody testing, there were no mortalities and the level of morbidity was significantly below what has been reported in general populations.

Keywords: Fibromyalgia; COVID-19; IL-6.

1. BACKGROUND

For decades a medical disorder that was given the name of fibromyalgia has at various times been used to describe what has been claimed to be either neurologic, rheumatologic and/or psychiatric in origin and which supposedly is a disease process that is purportedly medically benign, often associated with traumatic or emotional injuries and frequently linked to a hypothetical “central pain amplification disorder.” Efforts have chiefly been made to investigate and define this disease by relying on “rule out” testing.

Fibromyalgia has historically been manifested by chronic complaints of diffuse pain and tenderness, marked fatigue, disturbances in sleep, “brain fog,” mental depression, gastrointestinal upset and distress, numbness and/or tingling in the extremities, 18-19 points of particular painful and tender areas in the body, frequent headaches, joint aches, leg cramps, restless legs and anxiety. It has been given a variety of names beyond fibromyalgia including fibrositis, non-articular rheumatism, the chronic fatigue syndrome, myodysneuria, fibromyocitis and muscular rheumatism.

As was detailed in research conducted by Behm, et al. [1] of the University of Illinois College of Medicine Department of Pathology, there are, in fact, unique immunologic patterns in fibromyalgia such that these experts and those associated per research published by Wallace et al. [2] demonstrated and documented that fibromyalgia is conclusively defined as an immune dysfunction disorder that stems from the inability of peripheral blood mononuclear cells to

secrete normal quantities of particular chemokines and cytokines. These are MIP-1 alpha, MIP-1 beta, IL-6 and IL-8. The latter was proven per statistically significant findings as were described by the aforementioned researchers and were also proven to not occur in rheumatologic/musculoskeletal autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus. The latter discovery became the basis of a clinically available blood test labeled the FM/a test.

Coronavirus disease 2019 (COVID-19) appeared in 2019 with its first reports transpiring in Wuhan, China. It has been noted to be a severe acute respiratory syndrome which can lead to life-threatening processes including pneumonia, multi-organ dysfunction and potential organ failure and marked immunologic responses. Numerous researchers have identified that associated with COVID-19 infections is a “cytokine storm” which has a predominate increased concentration of the cytokine of IL-6 and to a lesser degree other cytokines, including IL-8. Among those who have delineated the latter clinical occurrences were Zeng, et al. [3] Mahmudpour et al. [4] Ghazavi et al. [5] Mc Elvaney et al. [6] Nagant et al. [7]

Because of the marked morbidity and mortality associated with COVID-19 infections, we believed that it was important to determine what responses to a COVID-19 infection would transpire in an FM/a test positive fibromyalgia patient in light of the chemokine and cytokine deficiencies that are associated with the latter disorder [8], particularly given the recent discovery of improved outcomes in COVID-19 patients who received IL-6 receptor antagonists [9].

2. METHODS

2.1 Study Groups

This study was approved by the University of Illinois at Chicago, College of Medicine Institutional Review Board and by the Sterling Institutional Review Board (Sterling IRB ID: 7984-BS Gillis). In the initial phase of this study, a total of 4,631 FM/a test positive fibromyalgia patients were screened via emails to determine how many of the latter group had experienced since January, 2020 any of the classic symptoms of a COVID-19 infection, including fever, shortness of breath, cough, a multi-day respiratory illness, a loss of sense of smell and/or taste, transient muscle or body aches, nausea, vomiting or diarrhea. We also asked that same group of 4,631 individuals whether they had been diagnosed with COVID-19 and/or hospitalized for COVID-19 and/or required mechanical ventilation in association with a hospitalization. While we received responses from all members of this group, only a total of 10 individuals reported having any of the aforementioned symptoms, no individual reported being hospitalized and no COVID-19 related deaths were reported in this group of 4,631 individuals. We interpreted the latter results as being atypical and therefore, we believed it would be necessary to evaluate a second cohort who were both tested for fibromyalgia via the FM/a test, as well as were tested for COVID-19 antibodies, all in an effort to accurately quantify the occurrence of COVID-19 in this population.

A total of 2,195 individuals were tested for COVID-19 antibodies. All of these fibromyalgia FM/a test candidates, based upon the FM/a test criteria had been off any immune system modulating agents for at least 30 days.

Patient and public involvement was limited to having all participants complete comprehensive medical questionnaires regarding their recent medical histories.

2.2 FM/a Test

The FM/a blood test as described by Behm et al. [1] requires the isolation of peripheral blood mononuclear cells which are then cultured with a mitogen, PHA. A residual supernatant undergoes a determination of cytokine and chemokine concentrations via a multiplex immunoassay based upon Luminex xMAP bead

array technology. The related sensitivity of this test is 99% and there is an associated specificity of 95%.

2.3 COVID-19 Antibody Testing

Every participant underwent a blood test determination to identify the existence of COVID-19 antibodies. The assays utilized the Abbott Architect SARS-Cov-2 IgG assay and a Luminex multiplex immunoassay bead array technology to identify antibodies to SARS-CoV-19 proteins, the Spike protein and the Nucleocapsid protein in human plasma.

3. RESULTS

A preponderance of the patients (68%) were 51 years or older. The study was based upon analyzing the incidence of COVID-19 disease in individuals documented to have fibromyalgia per a positive FM/a test. A total of 2,195 patients tested positive per the FM/a test. Of that group, 87% were female and 13% were male. They ranged in age from 18-89, see Table 2 regarding the breakdown in ages and ethnicity.

Regarding the 2,195 patients, a total of 82 patients were found to have evidence of COVID-19 antibodies. That makes for a percentage of 3.7%.

Table 1 identifies the characteristics of the 82 COVID-19 antibody positive individuals. They ranged in age from 18 to 89. Of this group, they characterized themselves as Caucasian, Hispanic, Native American Indian or Black. Only 4 were Hispanic and only 4 were Black.

Table 1. Ethnicity of COVID-19 antibody test positive patients

Ethnicity	Qty
Caucasian	73
Hispanic	4
Black	4
Native American	1

Of the 82, 42 had been diagnosed to have COVID-19 by a personal healthcare professional. Of the 82 who were detected to have COVID-19 antibodies, 23 had no symptoms. Of the 82, only 1 was hospitalized and that individual spent eight days on a mechanical ventilator and had no residual or permanent symptoms. There were no COVID-19 related deaths.

Table 2. FM/a test positive patient population

Ethnicity	Qty	%
Hispanic	223	10.15%
Caucasian	1702	77.56%
Black	136	6.19%
Asian	96	4.37%
Other	38	1.73%
Gender		
Male	291	13.25%
Female	1904	86.75%
Age Groups		
18-30	57	2.61%
31-40	248	11.28%
41-50	403	18.37%
51-64	784	35.77%
65+	703	32.04%

4. DISCUSSION

It is universally acknowledged that the coronavirus disease 2019 (COVID-19) has caused a pandemic with life-threatening complications. As of this date, per the US CDC Covid Data Tracker, approximately 74+ million individuals on a worldwide basis have been recorded to have experienced a COVID-19 infection, per CDC Morbidity and Mortality Weekly Reports. Related deaths have reached approximately 1.65 million. In the United States, more than 17 million Covid infections have been identified. The total deaths ascribed to COVID-19 in the United States has reached more than 500,000 though approximately twice that number is suspected to have actually succumbed. That makes for an incidence among the US population with COVID-19 at 5%.

We were interested in determining whether a documented immune deficiency disorder, i.e., FM/a test positive fibromyalgia, would become especially susceptible to COVID-19 and its particular immune system response that has been defined as a “cytokine storm” which is predominately affiliated with the cytokine of IL-6 and to a lesser extent the chemokine of IL-8. This issue became especially important when research was published that showed improved outcomes in COVID-19 patients who were treated with IL-6 receptor antagonists [9].

As has been already noted, of the 2,195 individuals with FM/a test positive fibromyalgia, we found the occurrence of a COVID-19 infection, as defined by the identification of COVID-19-specific antibodies, to only be 3.7% versus a US national predicted level of 5.0%.

Additionally, in the cohort we studied, while there was an expectation of some deaths, zero (0) actually occurred.

According to the CDC, a total of 63,152 laboratory-confirmed COVID-19 associated hospitalizations per day were reported between March 1, 2020 and October 17, 2020. The overall cumulative hospitalization rate was 193.7 per 100,000 population. Using those numbers, we would have expected far more than just one person in our cohort to have required a hospitalization but that did not transpire.

Based upon these statistical findings in our cohort, we believe the following to be evident.

Individuals with an immune deficiency disorder as defined as FM/a test positive fibromyalgia appear to be less susceptible to the near fatal and fatal complications associated with cytokine storms that have been detected in COVID-19 infections. We surmised that such a conclusion would be borne out after doing a screening of 4,631 such individuals. That indeed was confirmed based upon the accomplishment of COVID-19 antibody testing in a second cohort of 2,195 individuals.

What also makes our findings particularly remarkable is the appreciation that the vast majority of patients who develop a COVID-19 infection and who are most vulnerable to hospitalization and/or death are those who are above the age of 50. In our study, the preponderance of the patients (68%) were 51 years of age and older with 32% of the patients being over the age of 65. Resultantly, one would have anticipated a greater likelihood of

hospitalizations and/or deaths among these individuals. However, the latter did not transpire. Resultantly, we are inclined to challenge various theories regarding how the immune system responds to the COVID-19 virus in FM/a test positive fibromyalgia patients and why they have what appears to be a unique reaction to this particular virus.

5. CONCLUSION

We believe that the inability to produce normal quantities of IL-6 and IL-8 appears to have an ameliorating effect and one that is consistent with the recently published findings of the REMAP-CAP investigators who used IL-6 receptor antagonists to improve COVID-19 patient outcomes. Unlike the latter which relates to a receptor process, our patient cohort relied on specific production patterns of IL-6.

We do not presume that individuals with FM/a test positive fibromyalgia are less susceptible to developing a COVID-19 infection. Perhaps their understanding of the potential risk of having FM/a test positive fibromyalgia has led them to be more precautious and more likely to adhere to recommended public health policies, including but not limited to social distancing and the wearing of nasal and mouth masks. We, instead, are concerned about whether these individuals, once having contracted a COVID-19 infection are less or more susceptible to the most severe complications associated with a COVID-19 infection. What was unexpected was the fact that neither old age nor ethnicity made any in this group more susceptible to developing a COVID-19 infection, hospitalization or death.

The practical implications of our findings include the appreciation that additional methods of therapy for COVID-19 infections need to be considered and tested and especially as it relates to attempts to achieve a reduced production of actual critical cytokines and chemokines. We also believe that until and/or unless effective preventive COVID-19 therapies become universally available (i.e., COVID-19 vaccines) consideration of utilizing individuals who have an apparent reduced susceptibility to the immune responses associated with COVID-19 may make them more suitable candidates to act as first responders since they would have the lowest potential risk for contracting COVID-19 and secondary medical complications.

We noted that among our cohorts neither age nor ethnicity could be identified as particular risk

factors which we believe is less the result of a reduced sample size and more associated with the overall reduced immune production patterns affiliated with FM/a test positive fibromyalgia.

ARTICLE SUMMARY

Question

Do the innate immune system deficiencies including Interleukin-6 associated with fibromyalgia have any impact on the body's response to a COVID-19 infection?

Strengths and Limitations of this Study

This study was designed as a clinical investigation to identify whether the immune system deficiencies associated with the production of certain chemokines and cytokines by peripheral blood mononuclear cells in patients with FM/a test positive fibromyalgia mitigate the effects of a COVID-19 infection. An evaluation was done of 7,375 FM/a Test proven fibromyalgia individuals in reference to their occurrence of COVID-19 infections.

- The strengths included the ability to rely on highly specific and sensitive test protocols to document evidence in patients of fibromyalgia and their immune system deficiencies including interleukin-6 in a confirmatory manner.
- Fibromyalgia patients have well-defined immune system deficiencies.
- Fibromyalgia patients are not susceptible to near-fatal and fatal consequences of a COVID-19 viral infection.

Meaning

Individuals with immune system deficiencies regarding particular chemokines and cytokines (MIP-Alpha, MIP-Beta, IL-6, IL-8) were documented to have a markedly reduced susceptibility to near-fatal and fatal potential consequences from a COVID-19 infection.

6. FUNDING

Epic Genetics and the Department of Pathology at the University of Illinois College of Medicine at Chicago shared equally in the costs to perform the patient testing.

DATA AVAILABILITY

All data relevant to the study are included in this manuscript.

STROBE STATEMENT

The study's design was as an observational study whose objective was to determine whether a known immune system deficiency disorder, fibromyalgia, had a unique response to a COVID-19 infection.

CONSENT

All participants consented to participate in this study.

ETHICAL APPROVAL

This study was approved by the University of Illinois at Chicago College of Medicine Institutional Review Board and by the Sterling Institutional Review Board (Sterling IRB ID: 7984-BS Gillis)

COMPETING INTERESTS

EpicGenetics offers the FM/a Test for diagnosing fibromyalgia. Bruce S. Gillis owns EpicGenetics and a patent for the FM/a Test.

REFERENCES

1. Behm FG, et al. Unique Immunologic Patterns in Fibromyalgia. BMC Clinical Pathology. 2012;12:25
2. Wallace D, et al. Cytokine and chemokine profiles in Fibromyalgia, rheumatoid arthritis and systemic lupus erythematosus: A potentially useful tool in differential diagnosis. Rheumatology International; 2015.
3. Zeng H, et al. Longitudinal profile of laboratory parameters and their application in the prediction for fatal outcome among patients infected with SARS-COV-2: A Retrospective Cohort Study. Clinical Infectious Diseases; 2020
4. Mahmudpour M, et al. COVID-19 cytokine storm: The anger of inflammation. Cytokine. 2020;133.
5. Ghazavi A, et al. Cytokine profile and disease severity in patients with COVID-19. Cytokine. 2020;137
6. Mc Elvaney OJ, et al. A linear prognostic score based on the ratio of interleukin-6 to interleukin-10 predicts outcomes in COVID-19. E Bio Medicine 2020;61.
7. Nagant C, et al. A score combining early detection of cytokines accurately predicts COVID-19 severity and intensive care unit transfer. International Journal of Infectious Diseases; 2020.
8. Noroozi R, et al. Altered cytokine levels and immune responses in patients with SARS-COV-2 Infection and Related Conditions. Cytokine. 2020;133.
9. REMAP-CAP Investigators: Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. NEJM; 2021.

© 2021 Gillis et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/66972>*