

Covid-19 and its Changing Clinical Manifestations

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ABSTRACT

Background: COVID-19 is the ongoing pandemic that is adversely affecting millions of individuals all over the planet. Many changes have been done in course of treatment of COVID-19 to rectify the flaws. Mutations can pose serious threat and constant monitoring is needed.

Summary: Mutations are the inevitable phenomenon shown by the virus. Novel coronavirus has reported several strains which has been originated from the original strain which was reported from the Chinese's province of Hubei. Mutations pose serious risks to the containment measures of the pandemic. Genome sequencing is used to identify the new strain of the virus. Treatments like HCQ, convalescent plasma therapy, Remdesivir etc. have become redundant and do more harm than good. Selective usage, if necessary, can be done to ensure less harms. Monoclonal antibody therapy is being said to be the next big thing in the treatment of COVID-19. Vaccination is currently the most useful tool available to mitigate the spread of the disease.

Conclusion: More genome sequencing should be done to ensure the identification of each and every strain that is being roaming with humans all over the world. Even distribution of the vaccines can help to eliminate the virus from the human life and prevent further mutations.

Key words: Covid-19, Mutation, Delta variant, Monoclonal antibody therapy, Vaccine, Remdesivir

HOW TO CITE THIS ARTICLE: Gaurav Soni, Swaroopa Chakole, Covid-19 and its Changing Clinical Manifestations, J Res Med Dent Sci, 2022, 10(1): 162-166

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Received: 19/10/2021
Accepted: 13/12/2021

INTRODUCTION

Coronavirus disease 2019 or COVID-19 is the viral infection that has been designated as pandemic by the World Health Organization (WHO). The disease infection is caused by the extremely contagious novel coronavirus which was named as such due to its structure resembling the shape of crown. Since its inception in Wuhan city of the Hubei province in China, it has spread all across the world seriously affecting millions of people disrupting lives and livelihood of them. It is an unprecedented health emergency that was not seen in past hundred years of human history. Last being the Spanish Flu during the First World War. As of June 12, 2021, 175,360,785 infection cases have been reported and 3,786,943 case fatalities related to COVID-19 complications has been registered [1,2]. The huge number is enough to tell its high transmissibility and fatal nature. Vaccines are out for immunization and till now 2,310,036,837 jabs has been administered all over the world [3]. The viruses are notorious for changing their structure also known as mutations [4]. They keep on mutating throughout their lifecycle. Most of the mutations are of minor nature, but few of them are major and seriously alter the

manifestation of the virus in patients. Currently many mutant versions of novel coronavirus are roaming across the world, giving rise to more lethal second wave or phase of the pandemic. As there is no treatment available for COVID-19 infection which can be readily used. Therefore, doctors are compelled to use and repurpose the available medicines. Usage of HCQ, plasma therapy, Remdesivir and so on have proved less effective and has created more complications than benefits [5]. New medicinal therapies such as monoclonal antibodies therapy which contain two different cloned antibodies are currently used in many instances and showing some positive results. Vaccines are approved and being rolled out, but uneven distribution is the cause of concern. Targeted delivery of the vaccines towards desired groups might help in easing up the burden. In this article, we have taken a holistic overview of all the above aspects in detail.

Mutations in Covid-19

More than one and half year has been passed but COVID-19 infection cases are still on rise and there is no elimination of the pandemic in near future sight. The ups and downs in cases which follows certain pattern is partly attributed to the virus behaviour. The change in virus structure and its mechanism is known as mutation [6]. Viruses are notorious for their mutations and kept mutating all along their stay in the host. Viruses are the

link between living and non-living organisms and needs host to activate itself. In COVID-19 pandemic the host is human being. In the initial period of the pandemic which was also called as first wave of the pandemic, the symptoms and clinical manifestation of the virus was different and constantly changing. It can be assessed changing symptoms from fever, cough and cold to diarrhoea, loss of taste and smell and so on. The mutation makes the virus function differently if the mutation is of major type, otherwise many mutations are of minor nature and can go unnoticed. Mutation in coronaviruses have long history. The previous outbreaks of SARS and MERS were caused due to mutation in non-lethal version of coronavirus. This resulted into deadly epidemics which affected thousands of people. But the major difference between those outbreaks and COVID-19 pandemic is that the latter one is extremely contagious and lethal. Especially the persons having underlain medical conditions or comorbidities are highly susceptible for developing severe clinical outcome which is also driving the case fatality rate higher [7]. In fact, no other event in the past hundred years of human civilization caused as much fatalities as COVID-19. Mutations requires a free run among large number of populations which then adapts itself to become more belligerent. The second wave or resurgence in many countries across the world is mostly due to the mutant version of the novel coronavirus. The mutant versions are also more transmissible and lethal therefore it increases the risk even more. The spike protein attached to the novel coronavirus like appendage changes, and this makes the new version of the virus. New spike protein attached speeds up the oxidation in the body and takes complete control of the protein synthesis which is essential for the proper functioning of the body, when entered in human. Vital proteins like proteins that makes the cell wall, cytoplasm and other organelle of the cell does not get adequately produced then patient can slip into severe clinical conditions. Some of the mutant versions are marked as variants of concern by World Health Organization (WHO) and other health authorities to watch the viral behaviour associated with such variants. L452R and E484K are considered as one of the major substitutions in the spike proteins of the novel coronavirus which has culminated to new more transmissible and lethal mutations like B.1.525, P.2, P.1, B.1.351 and B.1.526.1, B.1.427, B.1.429. The former contains E484K, and latter contains L452R substitutions [8]. The current and lethal version is B.1.617 which is wreaking havoc in countries like India. It also has sub variants which are B.1.617.1 and B.1.617.2 which are identified in samples in United Kingdom and Brazil which are also reeling under pressure of increased infection cases. A lot of complications and name calling attached to current naming conventions of the variants of novel coronavirus has prompted WHO to come up with more suitable and easy nomenclature so that the current stigmatization of a country where the variant first found can be stopped and it is easy to report for the presspersons about the virus. Although previous alphanumeric nomenclature will stay as it is and can be

used by the scientists and researchers for studies. Two broad blocks of Variants of interests and variants of concern has been carved out and variants are placed according to their category. Variants of interests are the variants of novel coronavirus which has greater transmissibility and capacity of community transmission and variants of concern are the variants which are extremely transmissible and deadly and is creating a widespread havoc across the world. The names are given from Greek alphabets. Currently there are four variants in variants of concern category which are B.1.1.7, B.1.351, P.1, B.1.617.2 and they are named as Alpha, Beta, Gamma and Delta respectively. All of these are behind the recent resurgence of infection cases of COVID-19 [9].

Clinical manifestation in second wave of Covid-19

The second wave is largely attributed to the mutations that occurred in the dull period of the pandemic after the initial phase of the pandemic. Lax and negligent behavior on the part of people was also a factor behind the huge tsunami like wave of COVID-19 infection. The first phase looked meek in front of second phase of the pandemic as the cases grew exponentially. Huge influx of infected patients made hospital infrastructure to collapse and helpless as all the resources were under severe strain. From beds to oxygen and even crematory grounds were not enough to bury the people who obtain fatal clinical outcome due to COVID-19 related complications [10]. Also, unlike the first wave, this time there are large number of post-COVID-19 complications has been reported and large number of them suffered fatal blow. Long COVID-19 is already looming, and people are experiencing the worst phase of the pandemic till date. The increased cases of acute respiratory distress syndrome (ARDS) made it more difficult to clinically manage the patients. Large requirements of oxygen support system were felt as high viral load among patients severely affected their lung functioning. The rapid multiplication of the virus in host also created multi-organ failure as the oxygen requirement of the body was not met by the lungs. Viral load was found to be moving all over the body. The angiotensin-converting enzyme 2 (ACE 2) receptors which are present on vital organs like lungs, heart, kidney, liver etc. acts as a gateway for the virus. Once these organs are directly affected via blood then the management of the patient becomes difficult. Comorbid patients are in worst position if they are infected [11]. Various underlying medical conditions or comorbidities are worsening the already grim situation. Majority of the patients having any comorbidity along with COVID-19 infection needs sophisticated medical attention like ICU care and oxygen support system. Some of the severely affected individuals are ending up on ventilator support system. Lungs are the primary organs that are being affected. It is a vital organ for the proper functioning of the body as it provides oxygen to all parts of the body. Hypoxia, dyspnea are common among old aged and comorbid patients which needs immediate attention. Most of them needs hospitalization. The cytokine storm in which body creates a huge antibody response which results in killing normal cells of the body which are vital

for living. The cytokine storm is suppressed by administering the steroids like dexamethasone and other competent drug which are showing great result by suppressing immune system response. But there is a deadly consequence that has been seen in several patients discharged from the hospital and others [12]. The occurrence of mucormycosis commonly known as black fungus due to its appearance is haunting the COVID-19 infected patients. In the first wave, the mucormycosis cases were less in number and case fatality rate was also low among patients. But in second wave the case fatality rate attached to the mucormycosis is 50-80 percent which is a serious cause of concern. Hospital acquired diabetes also saw surge in its number as undue administration of steroid made sugar levels abnormal in patients. This has resulted in occurrence of diabetes in patients who never had one prior to the COVID-19 infection. Lack of cleanliness around the patients, over administration of steroids are some of the causes behind the large number of mucormycosis patients. Almost 90-95 percent patients of mucormycosis reported diabetes mellitus which is pointing towards interesting trends. Although it is not contagious like COVID-19, but one should be cautious as it can transmit itself through intimate contact with affected person [13].

As the pandemic evolved over more than a year, the clinical manifestation among patients also changed over the course. Therefore, it was necessary to reevaluate the therapeutic interventions that are in use. There has been major change in treatment course which was mandated by the circumstances and viral behaviour. The craze about hydroxychloroquine went down as no major improvement or efficacy was seen among patients. Some of the patients got relief from the ailments after administration of HCQ but it was largely a trial drug. Plasma therapy was another hyped method of treatment in which the plasma component of the blood of the COVID-19 recovered patient was given to severely ill COVID-19 patients in the hope of exploiting the benefits of the antibodies of the former. It was neither successfully nor failure as some of the population got relief from it. But the other factors associated were of serious nature. First there was a mental pressure on the recovered patient to donate the plasma who in most cases was severe fatigued and tired. Secondly fear of reinfection was also there due to lack of knowledge. Finally, some researchers blame the plasma therapy for deadly mutations that happened and are wreaking havoc all over the world through second wave. It is suspected that plasma infused in infected patients facilitated the mutations in novel coronavirus which resulted in inception of more lethal variant. After seeing that benefits are outweighed by the harms it done, it has been discontinued as a treatment of COVID-19 in many countries. The decision was prompted by irrational and misuse of the convalescent plasma therapy which tremendously increased the pressure on blood banks. In some cases, non-COVID-19 was in wait to receive plasma due to unnecessary usage in their COVID-19 counterparts [14].

Drugs like Remdesivir, Favipiravir and Fabiflu were all over on news. It was widely recommended by the doctors and was used for the course of treatment. The undue usage and prescription of drug has soared its prices several times. But no significant improvement in patients during its hospital was seen among majority of patients. On the contrary, hoarding and stocking of drugs was rampant and black marketing of drugs resulting into increased cost of drugs had drained the relative of the patients. Hundreds of kilometres of travel was undertaken by many relatives of the patients in search of the so called magic pill. But now almost 90 percent of the prescription has been done away with and usage in mild cases has been restricted. Self-medication is highly dangerous as it has consequences [15].

The introduction of new treatment called monoclonal antibodies therapy also known as cocktail therapy is gaining grounds as it is showing some promising results. As the name suggests they are the clones of the antibodies which targets one specific antigen. The antigen present on the spike protein of the novel coronavirus is covered by the antibodies so that it does not gets attached to the ACE 2 receptors of the organs. Casirvimab and imdevimab are the two laboratory manufactured antibodies which specifically targets the SARS-COV-2 spike protein. Severe to critical patients has been given such mix of medicine and it is found that it is possible to discharge the patient from the hospital shortly after the administration of the monoclonal antibody therapy. The harms of immunomodulatory, medicines such as steroids like dexamethasone, which are occurrence of mucormycosis can be eliminated if the monoclonal antibody therapy is administered [16].

Vaccination for Covid-19

So far no treatment has been establishes as the designated treatment course for the COVID-19. Doctors and medical professionals along with researchers are still trying hard and are administering drugs on trial-and-error basis. First the HCQ made headlines but found to be ineffective, then plasma therapy and now Remdesivir. All these treatments have their limitations and sometimes side effects among COVID-19 infected patients. Therefore it is important to highlight the importance of preventing the disease from happening at first place [17]. It will be tremendously beneficial to all the stakeholders as health care infrastructure has been collapsed in most parts of the world due to huge influx of the patients. Medical professionals are overworked and many of them lost their battle to COVID-19. Therefore it is necessary to follow all the protocols and guidelines which is issued by World Health Organization (WHO). Vaccine is one of them [18]. Vaccines are the preventive measure that helps in preventing worse outcome of the disease. Many vaccine candidates have been approved all over the world. Vaccination drives has been started all over the world to immunize the people from getting infected. In the first phase, all the health care professionals were immunizing so that they can work fearlessly as they are the first point of contact of the infected patients. Then

came the elderly and comorbid people who are in the high-risk category of the population. But as the resources are not equally distributed around the world, many low- and middle-income countries are fearing that they will get vaccine only after 2-3 years due to hoarding by developed countries. WHO led vaccine distribution alliance is gaining traction and acquiring dosage for these countries, but the pace is slow? As we know that, the more virus gets to roam through humans, the more it is prone to mutation which can create further complications as some mutations can evade the protection given by vaccines rendering vaccines ineffective. Therefore, simultaneous vaccination is necessary to eliminate the disease from this ultra-globalized world. Shortage of vaccines are the real issue, and it can be addressed by targeted vaccination. Those who are in high-risk category be vaccinated first so that the burden on the health care infrastructure is reduced by some extent. In one study, it is claimed that there is no point vaccinating the infected individual recovered from COVID-19. The antibodies prepared by the body are extremely effective and are superior to the vaccine induced response. It lasts or 5 to 7 months post infection. Therefore, those who are not infected should get priorities so that majority of the population is protected from the infection. The chance of reinfection is extremely less as successive infection is fought by the immune system very well due to memory they created in last infection. Although the study is not peer reviewed yet and in preprint stage. More broad-based study can shed more light on this crucial aspect [19].

COVID-19 is going nowhere at least for some period ahead, therefore we need to be extra cautious. Mutations are inevitable and happens all the time. Increases frequency of genome sequencing of samples arriving especially from foreign land can be done so that all the record keeping of the recent strain can guide the fight against COVID-19 [20-22]. The new nomenclature can reduce ambiguity and complexities. Especially connecting the viral strain to certain geographical area may prove detrimental towards them. The new nomenclature offers lucid and easy names for the widely spread variants which can be taken up by media persons to report. Various therapies need regular feedback assessment so that necessary changes can be made. The efficacy of the therapy must be regularly assessed to bring on changes conducive to elimination of COVID-19 [23-26].

CONCLUSION

New therapies which shown some promising results should be tested more thoroughly to pin point their benefits. Vaccination drives needs mass awareness as there can be seen vaccines hesitancy among people especially those who are illiterates or semi literates. Any kind of misinformation regarding vaccines should attract hefty charges so that the persons spreading fake news is deterred. Vaccine shortage is a global phenomenon as producing jabs equal to total human population on earth is a humungous task. Hence it is advisable to administer

the vaccine to the high-risk groups first so that the burden on health care infrastructure can be lessen. The efficacy of vaccines among recently infected and recovered patients of COVID-19 needs to be evaluated as antibodies made by the body naturally might provide some shield from reinfection for considerable amount of time. These vials then can be diverted to those who are still not infected by the COVID-19.

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