The Paradox of COVID-19 in Sub-Saharan Africa: Why it is More Unethical not to Investigate Low Dose Radiotherapy for COVID-19

Seyed Alireza Mortazavi[1], Joseph J Bevelacqua[2], James S Welsh[3,4], Seyed Jalil Masoumi[5], Batool Faegheh Bahaaddini Beigy Zarandi[6], Abdolkarim Ghadimi-Moghadam[7], Masoud Haghani[8]*, Seyed Mohammad Javad Mortazavi[9]

[1]MD, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]PhD, Bevelacqua Resources, Richland, WA, United States
[3]MD, PhD, Department of Radiation Oncology, Stritch School of Medicine, Loyola University, Chicago, Illinois, United States
[4]MD, PhD, Department of Radiation Oncology, Edward Hines, Jr. VA Hospital Hines, Illinois
[5]MD, PhD, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[6]PhD, Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[7]MD, Pediatric Infectious Ward, Yasuj University of Medical Sciences, Yasuj, Iran
[8]PhD, Department of Radiology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
[9]PhD, Department of Medical Physics and Engineering, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

An accumulating body of evidence shows that various ethnicities are differentially affected by SARS-COV-2 infection. Moreover, some evidence shows that due to the vaccine inequity and millions of people living with HIV, a major catastrophe could occur in African countries that possibly affects the whole world. Given the possibility that Neanderthal genes confer a slight increase in susceptibility, this difference, at least to some extent, might possibly decrease the risk of the emergence of new SARS-CoV-2 variants among black people in Africa. Recent studies show less death and fewer cases among the ethnic group classified as "Black Africans". Although Neanderthal DNA might explain some differences in morbidity and mortality of COVID-19, a multitude of confounders complicate things to where drawing definite conclusions is hard or even impossible. Using selective-pressure-free treatments (e.g. low dose radiotherapy) for COVID-19 pneumonia would be of crucial importance everywhere, but particularly in sub-Saharan Africa, where "long COVID" in millions of people with HIV paves the road for the more frequent emergence of new variants.

Keywords

COVID-19; SARS-CoV-2; Africa; WHO

Introduction

Dr Tedros Adhanom Ghebreyesus, the Director-General of WHO in his opening remarks at the media briefing on COVID-19 (14 September 2021) stated that while more than 5.7 billion COVID-19 vaccine doses have been administered worldwide, only 2% of those vaccines have been administered in Africa [1]. He also addressed the vaccine inequity and its potential impacts on the global social and economic disruption as well as the emergence of new SARS-CoV-2 variants, in particular those with increased transmissibility and viral virulence as well as immune escape, or pathogenicity: "*This doesn't only hurt the people of Africa, it hurts all of us. The longer vaccine inequity persists, the more the virus will keep circulating and changing, the longer the social and economic disruption will continue, and the higher the chances that more variants will emerge that render vaccines less effective"*[1].

While Dr Tedros Adhanom Ghebreyesus has brought up a very impor-

*Corresponding author:
Masoud Haghani
Department of Radiology, School of Paramedical Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: m.haghani4744@yahoo.com

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tant point regarding the consequences of vaccine inequity, there are reasons that we believe the risk of the emergence of new variants in Africa may be lower than current estimation. Some evidence shows a major catastrophe could occur in African countries that could affect the whole world, as most people in poor countries are not expected to be vaccinated in the very near future. However, Nguimkeua and Tadadjeu have reported that the number of COVID-19 cases in Sub-Saharan Africa is lower than expected [2]. Although currently, factors such as low median age and the small percentage of vulnerable old people are believed to be involved in low morbidity and mortality of COVID-19 in Sub-Saharan Africa compared to other regions of the world [3], we believe that the relatively smaller percentage of Neanderthal DNA in black people in sub-Saharan Africa may also be involved. Needless to say, while the higher proportion of Neanderthal DNA may be hazardous to many populations and a paucity of it relatively protective, it cannot be ruled out that other hazards may apply to Africans that may even override the protective effect of the paucity of Neanderthal DNA in their genomes. These hazards include the social and economic confounders that go along with ethnicity differences.

The AIDS Issue

As reported in a case report published as a preprint in MedRxiv [4], in South Africa a female 36 y old patient with advanced HIV who carried SARS-CoV-2 for 216 days, showed accumulation of 32 mutations of the SARS-CoV-2. Among these mutations, 13 were in the spike protein, which may enable the virus to escape the immune system. The remaining 19 mutations could alter the virus's behavior [5].

According to WHO, in 2018 Sub-Saharan Africa was the most affected region by HIV, with more than 25 million people living with that virus [6]. Moreover, about two thirds of the world's new HIV infections occurred in this region, where in the same year 470,000 people died from AIDS-related diseases [6]. Given this consideration, this population can be a permanent source of viral mutations.

Neanderthal DNA

Zeberg and Pääbo in their paper published in Nature in 2020 [7] have shown that the Neanderthal haplotype may be a great contributor to the risk of COVID-19 in some populations. They reported that the COVID-19 risk is conferred by a genomic segment of ~ 50 kilobases that is inherited from our Neanderthal ancestors. While outside Africa, all people carry around 2-3% Neanderthal DNA, *"Among the individuals in the 1000 Genomes Project, the Neanderthal-derived haplotypes are almost completely absent from Africa, ..."* [8]. Mortazavi et al. have recently addressed the possible role of Neanderthal genes in the high rates of COVID-19 in Iran [9]. They have also discussed different Neanderthal haplotypes which either makes people susceptible or resistant to COVID.

Interestingly, the data published in a recent paper [10] clearly show less death and fewer cases among the ethnic group classified by the authors as "Black Africans". In this study the adjusted hazard ratio (95% CI) for COVID-19 death after vaccination in "Black Africans" was 0.45 (0.17 to 1.21) compared to 1 for the "White" ethnicity group. Moreover, the adjusted hazard ratio for COVID-19 hospital admission after vaccination in "Black Africans" was 0.72 (0.41 to 1.26) compared to 1 for the "White" ethnicity group [10]. Due to the absence of statistical significance in these numbers, confirmation with larger sample sizes is required. The recently emerged omicron variant (B.1.1.529) is presently circulating in Southern Africa. The epidemiology and virulence of this strain among those with and without "significant" amounts of Neanderthal DNA (e.g. over 1%) may be instructive. Patterns of spread and clinical severity of omicron could test the hypothesis that certain Neaderthal

genes offer increased susceptibility. Figure 1 shows how the low proportion of Neanderthal DNA and millions of patients with HIV/AIDS in Sub-Saharan Africa influence in opposite directions the likelihood of the emergence of new SARS-CoV-2 variants in this region.

What can be Done in Africa?

A key solution for the risk of the emergence of new SARS-CoV-2 variants in Africa, and indeed everywhere in the world, is abandoning any treatment methods that exert a significant selective pressure on the virus (e.g. using antivirals) [11]. Given this consideration using "selective pressure"-free treatment methods such as the use of low-dose radiation therapy (LDRT) [12-15] may help healthcare professionals and public health authorities effectively control the pandemic. As a cytokine storm with increased levels of pro-inflammatory cytokines (e.g. IL-6 and TNFα) is involved in the pathogenesis of COVID-19 pneumonitis, appropriate LDRT methods have the capacity to modulate excessive inflammatory responses by downregulating pro-inflammatory macrophages and upregulating anti-inflammatory macrophages (IL-10, TGF β1) and NK T cells [16, 17]. In addition, controlling bacterial co-infections is among other mechanisms behind the therapeutic effects of LDRT. Although some of the LDRT clinical trials conducted so far had methodological problems [18, 19], the overall results show that this method can be introduced as a safe treatment with promising efficacy [20]. As addressed by Cuttler et al. it is unethical not to investigate radiotherapy for COVID-19 [21]; this might be even more unethical in sub-Saharan Africa, where long COVID in millions of people with HIV paves the road for the emergence of new variants.

In summary, reports show that the impact of the COVID-19 pandemic in Sub-Saharan Africa still remains significantly lower compared to the Americas, Europe and Asia. Although factors such as low median age are reported to be involved in sub-Saharan Africa's lower COVID-19 death rates, we believe that the significantly lower percentage of Neanderthal DNA in African ancestry may play a role in this issue. Therefore, in any estimation of the risk of the emergence of new variants in Africa, potential contribution of lower Neanderthal DNA proportion should be taken in to account.

Authors' Contribution

Ali Reza Mortazavi conceived the idea. After group discussions, Ali Reza Mortazavi, Masoud

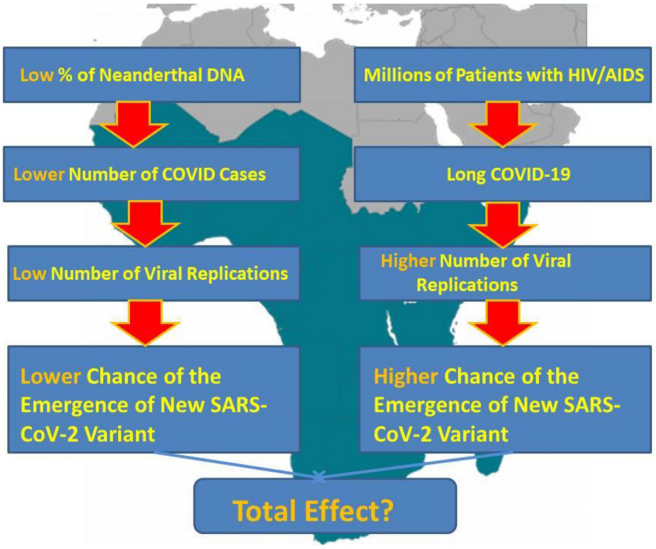

Figure 1: In Sub-Saharan Africa the low proportion of Neanderthal DNA and millions of patients with HIV/AIDS oppositely affect the likelihood of the emergence of new SARS-CoV-2 variants in this region.

Haghani, Joseph J Bevelacqua, and James S Welsh further developed the idea and drafted the manuscript. Seyed Mohammad Javad Mortazavi, Seyed Jalil Masoumi, Batool Faegheh Bahaaddini Beigy Zarandi, and Abdolkarim Ghadimi-Moghadam assisted in revising the manuscript. All the authors read, modified, and approved the final version of the manuscript.

Conflict of Interest

None

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