RESEARCH ARTICLE

Can CCR5 delta 32 mutation be a proof of possible HIV participation in the "Black Dead" epidemic?

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ABSTRACT: It is generally accepted that human immunodeficiency virus (HIV) is the etiological agent of acquired immune deficiency syndrome. According to this claim, HIV was transferred to humans from contact with monkeys around 35-50 years ago. However, this claim has not been sufficiently confirmed statistically and epidemiologically. The spread and incubation period and other symptoms of the plague epidemic have led to the theory that Black Death may have been caused by hemorrhagic viruses. Having examined detailed historical data, we have concluded that the bacterium Yersenia pestis was an infectious agent in the epidemic, together with another agent which we suggest was HIV. Our considerations are strongly supported by the CCR5 delta 32 mutation, which protects against HIV infection and has been present in the Caucasian population for over 2000 years. The combination of two infectious agents led to the devastation of the Black Death, the removal of HIV carriers, and an increase in the number of CCR5D32 mutations in the Caucasian population. In sub-Saharan Africa, this epidemic and subsequent sanitation process did not occur, resulting in a much higher level of HIV genetic information in this population.

Key Words: *AIDS; HIV; Black death epidemic; Yersinia pestis; CCR5D32 mutation; Caucasian population; Sub-saharan africa*

INTRODUCTION

The notion that HIV was transferred from monkeys to humans in Africa around 35 to 50, or even 100, years ago is generally accepted [1-10]. It is also widely accepted that Africa is the geographic source of HIV, with AIDS recognized as a logical consequence of HIV infection. This claim is supported by the fact that most HIV-positive individuals are currently in Africa. Such a viewpoint can only be disproved by developing new hypotheses that are sufficiently convincing, but none have so far been presented.

To move on to this problem, let's go deeper into human history and analyze how the health of the human population has evolved. The quality of human health has changed over time, with the biggest changes occurring during a series of epidemics in Europe, Africa, and Asia [11]. The first of these dates back to the Peloponnesian War in 525 BC. Later, Justinian's plague in 541 AD killed 100 million people, representing 40% to 50% of the Roman (Byzantine) Empire. The agent(s) responsible for these epidemics is unknown. The largest known plague epidemic, the Black Death, was caused by the bacterium Yersinia pestis. This epidemic broke out in Italy in 1346, from where it spread throughout Europe and then to Asia, decreasing the population by 40% to 50%. At least 60 million people died in China, as well as 50 to 70 million in Europe. In the Middle East, the epidemic wiped out 30% to 40% of the population [12]. It did not affect people from the Americas or sub-Saharan Africa. This intense, long-standing epidemic lasted until the 18th century, but could also be considered a 'sanitation' process. The most common victims of the epidemic were people suffering from malnutrition, and those with weakened immune systems. In comparison, the survivors had better health and overall life expectancy increased after the epidemic, when it was not uncommon for people to live to 70 or 80 years of age; this was very rare prior to the epidemic.

CASE REPORT

CCR5 delta 32 mutation in "black dead" epidemic

Survived individuals carrying the mutated delta 32 allele of the CCR5 coreceptor gene that is predominantly expressed in T cells, macrophages, dendritic cells, eosinophils, microglia and a subpopulation of either breast or prostate cancer cells [13,14]. The CCR5 protein belongs to the beta chemokine receptors family of integral membrane proteins [15]. It is a G protein–coupled receptor which functions as a chemokine receptor in the CC chemokine group. HIV-1 most commonly uses the chemokine receptors CCR5 and/or CXCR4 as co-receptor to enter target immunological cells [16]. These receptors are located on the surface of host immune cells whereby they provide a method of entry for the HIV-1 virus to infect the cell [17]. The HIV-1 envelope glycoprotein structure is essential in enabling the viral entry of HIV-1 into a target host cell. The envelope glycoprotein structure consists of two protein subunits cleaved from a Gp160 protein precursor encoded for by the HIV-1 env gen - the Gp120 external subunit and the Gp41 transmembrane subunit.[17].

CCR5 Δ 32 is a 32-base-pair deletion that introduces a premature stop codon into the CCR5 receptor locus, resulting in a nonfunctional receptor [18,19]. This mutation is known to protect against Y. pestis infection as well as pox virus and HIV infection [20-31]. CCR5 is required for M-tropic HIV-1 virus entry [32].

Individuals homozygous (denoted Δ 32/ Δ 32) for CCR5 Δ 32 do not express functional CCR5 receptors on their cell surfaces and are resistant to HIV-1 infection, despite multiple high-risk exposures [20]. Individuals heterozygous (+/ Δ 32) for the mutant allele have a greater than 50% reduction in functional CCR5 receptors on their cell surfaces due to dimerization between mutant and wild-type receptors that interferes with transport of CCR5 to the cell surface [21]. Heterozygote carriers are resistant to HIV-1 infection relative to wild types and when infected, heterozygotes exhibit reduced viral loads and a 2-3 year-slower progression to AIDS relative to wild types [18,20,22]. Heterozygosity for this mutant allele also has shown to improve one's virological response to anti-retroviral treatment [23]. Homozygous carriers of the mutation are also resistant to M-tropic strains of HIV-1 [32]. Because the entry of HIV-1 into cells requires CD4 receptor and either CXCR4 or CCR5, individuals carrying CCR5D32 on both alleles of CCR5 are resistant to HIV-1 infection. CCR5 Δ32 has an (heterozygote)

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allele frequency of 10% in Europe, and a homozygote frequency of 1%. CCR5D32 mutation has a relatively high frequency in the Caucasian population, but is absent from individuals in sub-Saharan Africa, East Asia, and the Americas [18,24-34]. Moreover, its absence was confirmed in most tribes in India [35]. This suggests that it is a single mutation that likely occurred following the divergence of Caucasian Africans from their ancestors andit was historically subject to positive selection. This is also supported by genetic analysis of binding, which indicated that the mutation has a homogeneous genetic background, occurred after divergence of Europeans from their African ancestor [12,18,25,34]. A mathematical model indicated that this mutation is at least 1500 to 2500 years old [12,24,26,33,36]. A study of ancient DNA at the University of Queensland reported the detection of CCR5D32 mutant alleles in four skeletons dated at 900 BC from a grave in Germany [33]. Finally, the CCR5 Δ32 allele has a unique geographical distribution indicating a single Northern origin followed by migration. A study measuring allele frequencies in 18 European populations found a North-to-South gradient, with the highest allele frequencies in Finnish and Mordvinian populations (16%), and the lowest in Sardinia (4%) [26].

Objections to the role of Yersenia pestis in the black dead epidemic. Scott and Duncan hypothesis.

The spread, incubation period and other symptoms of the plague epidemic have led the epidemiologists Scott and Duncan and the medieval historian Kohn proposed to the theory that the Black Death was caused by hemorrhagic viruses, such as Ebola, rather than bacteria such as Y. Pestis [33]. Scott and Duncan advocated that Ebola resistance genes are very widespread throughout Europe, and that the virus can enter cells of the immune system using the CCR5 coreceptor [31]. They also argued that the plague spread much faster than usual epidemics, and that the incubation time was unusually long [33,37-39]. Longe incubation times (up to 30 days) allow the carrier to travel further and infect more people. If the primary vector was a human, such distances could be around 3 miles a day. Indeed, the Black Death spread remarkably rapidly: from Sicily to the Arctic Circle in less than 3 years during which it covered vast areas of Europe. This is in complete contrast to a bubonic plague epidemic which moved very slowly [40]. The black rat, the plague vector, has a home range of 100 m and rarely strays outside of this [39]. The plague has also been documented in parts of Europe where rats did not live, such as Iceland [41]. Epidemiological studies showed that the plague was transmitted from an infected human to a human susceptible to infection diseases within a 4-m range [38]. The plague epidemic in Europe served to strengthen the frequency of the CCR5D32 mutation in the area, with the Black Death increasing it to around 10% of the European population [42,43]. In Finland and northern Russia the increase was 16% to 20%. Importantly, mutations have not been detected in sub-Saharan Africa, America, and Southeast Asia where infections have not occurred [20,35]. The fact that the allele is present in such a high percentage of one population but was absent from another population suggests that selective pressure was strongly in favor of this allele. The most likely source of this genetic pressure is the Black Death itself.

The relationship between CCR5D32 and the Black Death mutation between 1346 and 1353 is described in detail by Stephens [34]. In Northern Europe and Russia where the population frequency of CCR5D32 was >10%, mortality levels were below 25%. In areas of southern Europe and the Middle East where the population frequency of CCR5D32 was below 6%, mortality rates exceeded 50%.

In addition to Yersinia Pestis, could other agents participate in the black death epidemic?

This statistical study suggests that CCR5 delta 32 mutation protected humans from the epidemic. The mutation bearers have resisted Yersenia pestis infection. This may indicate that other agents than Yersenia were more important in the epidemic. Since the protection of the mutation against Yersenia pestis is not sufficiently confirmed, another more important and aggressive agent has entered the game. Based on our considerations and previous results, this agent was HIV. Therefore, mutation carriers survived because they were protected from HIV, which was more important for their survival than Yersenia pestis infection. This allows us to say that the primary role in the epidemic was played by HIV. And this is a very important statement. The question that remains is how has the CCR5D32 mutation that induces HIV resistance existed for so long in the human population? Is it possible that the human population was in contact with HIV before the 20th century? There are several reasons to reflect on this, especially when considering the intensity of the Black Death epidemic. First, it is estimated that there were more than 200 million victims in Europe and Asia, the most in history. Second, it is likely that the epidemic was a combination of diseases caused by agents such as Yersenia pestis and (an)other, still unknown, agent(s). If we do not accept the standard viewpoint about the origin of HIV, we might reach the conclusion suggested by Scott and Duncan. Indeed, if we consider other viruses as possible agents, we should include HIV because the CCR5D32 mutation clearly provides protection against infection.

Duncan and Scott do not assume that the CCR5D32 mutation prevents Y. pestis from entering T cells [33]. This was also supported by the fact that CCR5 co-factor binding glycoproteins such as HIV gp120 and HIV gp41 and bacteria such as Y. pestis have no glycoproteins [44,45]. This option was tested by infecting wild-type and CCR5-deficient mice with Yersenia pestis. No differences in the survival of the two groups were found, as seen in a study by Mecsas et al. [29]. However, a significant reduction of Y. pestis absorption by CCR5-deficient macrophages was observed in vitro. These results indicated that the role of CCR5 in infection may be more complex than previously thought, and that Yersenia pestis may infect mammalian cells by other means. Epidemiologists very rarely consider the role of the CCR5D32 mutation in the true pox epidemic because it does not spread, remaining in one area [33]. However, some experts advocate a theory that highlights the effect of smallpox in a given epidemic [45]. They surmise that smallpox virus has been infecting humans for thousands of years, with the oldest epidemic believed to have occurred long before 1000 AD. If the receptor for the pox virus is CCR5, then smallpox is a candidate for the selection pressure responsible for the fixation of the CCR5D32 resistance allele in the Caucasian population [44,45]. This option has not yet been tested and it is not possible to be proven experimentally at the present time.

RESULTS

Hypothesis presentation

The claim that HIV was transmitted from African monkeys to humans through random contacts 35 to 50 years ago is not sufficiently confirmed epidemiologically or statistically. If we consider the evolution of human health, the biggest changes occurred during epidemics, which have left a strong footprint on the current status of health. The Black Death epidemic of the 14th century has most affected human health. It was also a form of sanitation that restored the microbial balance of the human body, and the health of the majority of the human population. The Black Death's course was epidemiologically unusual, so it is assumed that other agents besides Y. Pestis were involved in its high mortality. Epidemiologists Scott and Duncan suggest that this was an Ebola-like virus. On the basis of our studies and results, we propose that this was HIV. We suggest that HIV has a human origin and that it has been an inseparable part of humankind since the beginning of our existence [46-50]. Moreover, its distribution in the population is uneven and differs among families.

We suggest that the microbial balance has been disrupted, in ways including intestinal dysbiosis, in the mid-20th century through the acceptance of antibiotics, drugs (including recreational), medicine, and lifestyle changes (such as anal sex). Additionally, bacteria and yeast containing extra genetic information in the form of phages, plasmids, and viruses attack T cells, leading to the collapse of the immune system. Has HIV been present in the human population since the beginning of its existence? There are important indications to this claim, particularly the presence of the CCR5D32 mutation. The role of CCR5D32 during the Black Death has not been discussed before because the existing dogma suggests that HIV only infected the human population in the 20th century. However, if this notion is rejected, the infectious agent may be considered to be HIV itself. We may propose several alternatives to the interaction of Y. pestis and the second agent, which could be thought of as HIV:

1. The first victims of the Black Death epidemic were people with a damaged immune system caused by violation of the microbial symbiosis in their body. Y. pestis particularly infected carriers of HIV genetic information. The immune system of these individuals was weakened by the systematic penetration of pathogenic genetic information, and the infection and lysis of

T cells. The outcome of this sanitation process was the destruction of carriers of HIV genetic information and the complete recovery of the Caucasian population. However, carriers of the CCR5D32 mutation survived this pressure, which increased the frequency of CCR5D32 to 10%, and to 15% to 20% in northern parts of Europe.

2. Y. pestis served as a helper to activate 'dormant' HIV in its carriers, followed by HIV amplification. After the penetration of HIV genetic information into the blood, T cells were infected and lysed, whereby the immune system collapsed and immunodeficiency followed. Because a considerable proportion of the population were carriers of HIV genetic information, the pandemic had devastating consequences.

3. The epidemic of the 14th century was a combination of Y. pestis and HIV infection agents. The epidemic was devastating because it led to the death of carriers of HIV genetic information. This notion corresponds to the mode of transmission — from human to human — and the rate and intensity of the epidemic, which differ completely from classical Y. pestis infection. HIV co-occurrence in the epidemic increased the frequency of CCR5D32 mutations in Caucasian populations. The importance of mutation CCR5D32 has been certified and may be used therapeutically in the development of models to induce resistance to HIV.

Historically, in sub-Saharan Africa individual communities have been geographically isolated, and lacking commercial and population exchange. As a result, there was no transfer of infectious agents, and this steady state lasted for many centuries. Because of the complete absence of an epidemic and subsequent sanitation process in this part of Africa, HIV genetic information was not eliminated from humans. This explains the much higher level of HIV there compared with other parts of the world. However, the situation changed in the middle of the 20th century, with mass rural–urban migration. Water shortages, poor sanitation, a lack of sanitary products, the use of antibiotics and drugs, and extreme sexual promiscuity have caused a sharp increase in a wide range of bacterial and viral diseases, including AIDS. Highly active antiretroviral therapy is expensive, so is not available for all HIVpositive individuals. Therefore, we propose that the prevalence of HIV in the population of sub-Saharan Africa could be reduced by administering probiotics to remove pathogenic microbes from the intestinal microflora.

In this context, we could also answer the basic, yet inadequately explained question:

Why did AIDS first appear in the United States and not in Africa, where HIV is thought to have originated?

To answer this question, let's go back to the 17th to 19th centuries. At that time, thousands of Africans were forcibly transported to America, where they worked as slaves on plantations. Many of them were HIV carriers because they did not cross the "sanitation process" as members of the Caucasus population. Only the healthiest and the lower-HIV bearers endured this burden. It was an indirect "sanitary process" of eradication of carriers with higher HIV levels, as the individual's health was the most important. Although living in difficult conditions in America, they did not express HIV because their strong immune system prevented it. The turning point came in the middle of the 20th century. Because many African-Americans lived in emergency conditions, they resorted to drug use, initially 'recreational', which was gradually being replaced by hard drugs. The process was also accelerated by the Vietnam War, where a large proportion of the soldiers were African Americans. The soldiers were in a great depression that was overcome by drug use, anal and homo sex. This impairment of the immune system followed "intestinal dysbiosis" and the expression of HIV genetic information. Thus, as a result of the failure of the immune system, they developed AIDS.

DISCUSSION

Evaluation of the hypothesis

On the basis of our findings and considerations, we have come to the conclusion that Y. pestis and HIV were both involved in the Black Death epidemic of the 14th century. It is the combination of these two agents that made the epidemic so devastating, and resulted in the removal of HIV carriers and the increase of the CCR5D32 mutation in the Caucasus population to 10%, or to 15% to 20% in some northern regions. The lack of epidemics and subsequent sanitation process in sub-Saharan Africa prevented the deletion of HIV genetic information from this population, and explains the absence of the CCR5D32 mutation.

On the basis of expert predictions it is likely that unless there is a radical change in the near future in Sub-Saharan Africa will die from AIDS 250-350 million people. This is a challenge for all of us. It is absolutely necessary to overcome all the taboos and dogmas and to seek new ways to reverse this forecast.

CONCLUSION

Consequences of the hypothesis

The submitted hypothesis enables many previously unanswered questions to be answered: the origin of HIV, the high rate of HIV mutations, the extensive HIV positivity in Africa, the link between AIDS and tuberculosis in Africa, the reasons for the first AIDS cases in America States and not in Africa, where HIV is thought to have originated, the presence of HIV in the reservoir after antiretroviral therapy, low level of detection of complete viral particles, but common detection of HIV sequences in AIDS patients. Confirmation of the presented hypothesis would bring new insights into AIDS and open up new possibilities in its diagnostics and therapy.

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CONFLICTS OF INTEREST

There is no conflict of interest.

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