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HYPOTHESIS

Manipulation of Sexual Behavior in Humans by Human Papilloma Virus

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Abstract. Parasites often alter the behavior of their host to facilitate transmission. Sexually transmitted infections in humans may offer an opportunity to explore this area further as the causative agents are under rigorous selection pressure to manipulate the sexual behavior of the host for their own evolutionary advantage. In recent time sexually transmitted pathogens like human immunodeficiency virus (HIV) and Herpes simplex have been speculated to induce similar changes in the human host. Human papilloma virus (HPV), which is leading cause of cervical cancers, may be the one of the best candidates to study such manipulations in humans. Limited modes of transmission and cultural constraints in orthodox societies where sexuality is still a taboo may put the virus under immense selection pressure to manipulate the host sexual behavior and large number of available mutational variants within the host may actually support the entire process. HPV which has evolved to spread through oral sex and open mouth kissing has been confirmed as the major culprit for the rising oral cancer cases in Western World. HPV has been also linked to breast and prostate cancer. HPV was found in many cases of Retinoblastoma among the children of India and USA which proves its ability to infect neurons too. Infection in brain provides with ample opportunity to manipulate neuronal circuits that may influence sexual behavior directly or indirectly. Considering the versatility of HPV to colonize various sites in Human Body and most recently human brain I hypothesize that HPV can manipulate sexual behavior in Humans when the chances of transmission are very thin even in the entire lifetime of the host.

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1. Introduction

Every infectious agent is programmed with two fundamental imperatives of survival and reproduction. The exploration of infectious diseases with such perspective can offer great insights for the better understanding of the sexually transmitted infections. Parasites often alter the behavior of their host to facilitate transmission to newer hosts [1]. One of the most fascinating and recent example comes from malaria causing protozoan Plasmodium falciparum. This parasite makes the infected human host more attractive for the mosquitoes to enhance its chances of transmission by frequent bites [2]. Toxoplasma gondii manipulates mate choice in the feamel rats by enhancing the sexual attractiveness of the infected males [3]. Viruses are no more an exception when it comes to manipulation of the host for their own advantage. One of the most cited example is that of the Rabies virus which infects the neurons in the limbic cortical areas of brain of the host and thus modulates the aggressive behavior for better transmission [4]. The chances of host sexual behavior manipulation in case of sexually transmitted infections caused by viruses are very high due to the intense selection pressure present in certain specific populations. The proposed hypothesis is intended to express the possibility of manipulation of such sexual behavior by viruses and microbes that are transmitted sexually in Human Subjects and HPV seems to be the candidate with the fairest chances of such manipulation.

2. Hypothesis

The high risk HPV strains (16 and 18 mainly) have been proved to be the major cause of cancers of cervix, vulva, penis and other reproductive organs [5]. HPV infection spreads mainly through sexual intercourse [5]. There are very limited non-sexual modes of HPV transmission available. Sexual intimacy, which includes open mouth kissing, is a major mode of transmission in case of HPV. HPV high risk strain infection has been recently found to play a major role in oral cancers which are directly associated with the rising trend of oral sex among the western youth [6]. The risk of developing oral HPV infection was found to increase with increase in number of lifetime oral or vaginal sex partners. It has also been reported that not only oral sex, but also open-mouthed kissing, was associated to the development of oral HPV infection [6, 7]. The virus has adapted to colonize in the oral cavity, thus has created a new opportunity to spread through juicy and open mouth kissing in case of partners having oral infection. The Virus can go a step further and can actually make people kiss more passionately with higher frequency to improve the chances of infecting new hosts to a great extent. The virus will adapt to colonize almost every site that may give it a selective advantage to spread to large number of new hosts which is evident from the HPV induced cancers of genitals in humans like that of vagina, vulva, anus and penis [5]. Recently high risk strains of HPV 16, 18 and 33 have also been detected in normal breast as well as the Cancer tissues across the world [8]. In many cases the HPV detected in the breast cancer tissue is among the women of younger age from countries like USA, Australia and Greece which have rising trend of multiple sex partners, Oral Sex and one night stand or casual sex [8-10]. The HPV positive breast cancer patients in Canada and Syria were also found to be significantly younger compared to the women with HPV negative

breast cancer [11-14]. Infection at younger age will give ample opportunity to the virus to infect large number of new hosts in the entire lifetime of the infected girl or women and thus may also lead to cancer of the infected organ in long run. The colonization of Breast tissue especially the outer surface and the nipple area among the sexually active young girls and women make lot of evolutionary sense. Breasts are one of the most intimately involved sites during sexual act and thus can help in spread of virus to very large number of new hosts especially when both of the couple has multiple sex partners. In many studies the women with breast cancer had earlier cervical infection of HPV and the HPV strain detected in the breast cancer tissue samples were the same that infected their cervical or genital region [15, 16]. It is very likely that after cunnilingus the male partners infect the breast nipples and surrounding area via hand and most probably through oral route with the same HPV strain that has infected the female cervix or genitals. Open mouthed kissing after cunnilingus may cause infection of oral cavity in women with the same HPV strain that has infected her genitals. The colonization of the breast nipples and surrounding area will lead to oral infection of the male counterparts and they can further infect some of their other female sex partners leading to a whole vicious cycle of infection benefiting significantly to the virus. It is very likely that virus may also manipulate the host sexual behavior in a way that facilitates transmission in regions where the chances of transmission are very thin due to some cultural constraints. The chances of such manipulations of sexual behavior are very high in the countries having conservative approach towards sexuality. In majority of the South Asian countries, mainly in India, Nepal, Bangladesh and others, sexuality still remains a taboo. The natives in such societies generally disapprove love marriage, premarital sex and having multiple sex partners unlike western countries. Majority of the population hardly prefer more than one sex partners post-marriage in their entire life. Nations with majority of Muslim population across the world, including those in South Asia, follow an ancient trend of male and female circumcision which has been proved to be highly effective in blocking the transmission of HPV and other sexually transmitted infections [17]. The pathogens in such case will have very scarce chance of infecting a new host even in the entire lifetime of its current host and it will eventually die if it fails to infect a new one. This type of cultural constraints create a very strong selection pressure on the virus to evolve with a trait that can manipulate sexual behavior of the host to increase its rate of transmission since the available modes for transmission narrow down in such conditions. As a manifestation of such manipulations it is very likely to find increased levels of testosterone in the infected men and that of estrogen in case of women. Infection of the brain may also lead to change in the sexual patterns of the host. The manipulation need not always arise out of neuronal infection in CNS as higher replication in target peripheral tissues along with the modulation of neuro-immunal pathways and further communication via hormonal signaling to CNS may also result in behavioral changes [18, 19]. The major advantage of increased sex hormone level in host is immunosuppression as it has been recently found that ovulating women are at greater risk of acquiring HPV and other sexually transmitted infections due to sudden dip in the immunity caused by higher level of serum estradiol that allows spermatozoa to survive the threat of an immune response and to fertilize an egg successfully [20]. Parasites are also capable enough to sense the physiological changes in the host and direct those changes to enhance their reproductive fitness [21]. DNA based viruses like HPV

may also produce substantial number of variants owing to factors like large population sizes, long infection time and hypermutation of the epitopes that can lead to significant evolution of the virus within the host [21].The HPV 16 which is a high risk strain known to cause cancer of cervix, genitals and extra genitals has recently been linked to prostate cancer and lung cancer [22, 23]. Considering the versatility of the virus to colonize diverse tissues in human body it will not be exorbitant to speculate that it can also colonize human brain and manipulate the neuronal regions regulating sexual behavior like amygdala, hypothalamus and others for its own evolutionary advantage. Another major advantage to the virus on Colonizing brain is the protection from the immune surveillance of the host and an opportunity for persistent infection due its immune privileged site status.

3. Documented Studies In Support of the Proposed Hypothesis

3.1. Host Manipulation by Viruses in Rodents and Primates

There are many examples in case of rodent and primate infections where viruses manipulate their host behavior by infecting the neurons in limbic system, hypothalamus and other regions of the brain. Viruses transmitted during the sexual act which often includes biting in many species are under very intense selective pressure to alter the host sexual behavior as the opportunities of transmission are quite less due to restricted availability of non-sexual modes. Borna Diseases virus induces aggression in rats by infecting the neurons in vomeronasal regions, olfactory bulbs and limbic cortical areas [24, 25].Herpes Simplex Virus induces the same effect in mice as that of BDV by regulating 5-HT and DA synthesis pathways in mice [26]. Higher aggression and wounding are often correlated with higher SIV infections in primates. The proximate mechanisms for such effect are infection of glial cells in basal ganglia and certain neurons in thalamus region of the brain. Feline immunodeficiency virus which infects cats manipulates their host in much similar way as SIV does in primates. Infections in the areas of brain like hippocampus, hypothalamus, thalamus, olfactory bulb, amygdala, frontal cortex and septum have been speculated to be responsible for higher aggressive and sexual behavior in rats infected with BDV [27-29]. Elevated serum testosterone levels and consequently enhanced aggressive behavior have been detected in mice infected with tick-born encephalitis virus [30]. Aggressive Norway rats infected with Hantavirus have been documented with lower 5-HIAA levels along with higher testosterone serum concentration [31].

3.2. Manipulation of the sexual behavior by Viruses in Humans

Host behavior manipulation in case of sexually transmitted diseases is one such phenomenon that makes lot of sense in the light of evolution. This field is still in its nascent phase when it comes to such manipulations in case of humans as scientists across the world have just started coming with some convincing illustrations like that done by the virus of genital herpes. Herpes virus has adapted to colonize oral cavity for rapid transmission through Juicy and passionate kisses or the one that includes exchange of saliva. Most importantly changing sexual behaviors are changing transmis-

sion dynamics in ways that will shape certain pathogens for faster transmission with culture playing pivotal role in the regulation of such transmission processes. This has particularly happened in the case for transmission of herpes viruses in response to recent increases in oral–genital sex in western culture. Other than this ganglion infection in genital herpes is speculated to alter the sensory input to sex organs leading to enhanced libido and thus higher probability of virus transmission [32]. Scientists from University of California, Berkeley have documented higher levels of testosterone among the HIV positive patients during their primary stages of infection in South Africa [33]. Elevated serum testosterone above normal standards may induce higher libido and thus can lead to higher mating frequency thereby increase the chances of transmission to other host. There are two major obvious rationales for this type of manipulations.

1). Evolutionary success of sexually transmitted pathogens depends on mating frequency of the host rather than its population density. Most of the STDS have been evolved to persistence as chances of host mating with different partners are quite less in small span of time. The hosts with the highest mating success are also at the highest risk of getting sexually transmitted infections [34]. Thus there is very high selection pressure on the pathogens to adapt in a way that facilitate their transmission by altering mating frequency.

2). RNA viruses like HIV have very high mutation rate per replication and thus there are more mutational variants available within the host for the evolution of desired trait [35].

3.3. The Bizarre Manipulations of the Toxoplasma Gondii

Toxoplasma gondii is one of the most extensively studied parasites for the host behavior manipulation hypothesis. Toxoplasma gondii infection in both mice and rats reverses the rodents' natural aversion to the smell of cat urine and causes them to instead "develop an actual attraction to the pheromones" [36]. This behavioral change is thought to be beneficial for the parasite as it can engage in sexual recombination only in the Cat intestines [36]. The manipulation also enhances the transmission of the parasite through the trophic route. Toxoplasma gondii does not stop here as it has been recently found to manipulate the mate choice among the female rats. Male rats infected with Toxoplasma gondii become more attractive for the uninfected female rats [37]. This leads to further transmission of the parasite from infected male to uninfected female and later to their progenies [38]. The proximate mechanisms behind the manipulation elucidated so far are associated with the higher levels of Testosterone in the infected males caused by enhanced expression of steroidogenic enzymes and LHR receptors in testes [38, 39]. Testosterone is also known to affect the fear response among the rats by binding to certain receptors in the limbic system that regulate this emotion [40]. Toxoplasma gondii manipulation of intermediate host behavior could be due to the parasite localizing in specific brain regions and the most likely brain regions are those associated with regulation of fear response [41]. Amygdala in brain is involved in fear processing and recent work provides a potential process for fatal feline attraction mediated by pathway that activates the amygdala. Modulation of the sexual arousal pathways in

the posterodorsal amygdala has also been reported. There are immense possibilities that the parasite may hijack this sexual attraction mechanism in order to override the rat's innate aversion to cat odor [41]. The specificity of these manipulations point towards targeted physiological manipulation rather than accidental or pathological manifestations of infection.

The parasitic protozoan Toxoplasma gondii infects about one-third of the population of developed countries and hence can be a good model to study the manipulation hypothesis in humans [42]. Toxoplasma -infected subjects differ from uninfected controls in the personality profile estimated with two versions of Cattell's 16PF, Cloninger's TCI and Big Five questionnaires [42]. Most of these personality defects progress with the increase in the infection time, suggesting that Toxoplasma influences human personality rather than human personality influencing the chances of infection [42]. Toxoplasma gondii infection increases the reaction time of infected subjects, which can explain the large number of traffic accidents found among the infected subjects reported in three retrospective and one very large prospective case-control study [42]. Recent studies have found that the male with the infection have higher testosterone levels and thus were found more attractive by the females when compared with the males without the infection. The exact proximate mechanisms behind the effect among humans are under investigation [42]. Raised or disrupted dopamine levels have been reported in both rodent and human Toxoplasma gondii infection and within human patients with schizophrenia [43-46]. Elevated levels of Dopamine have also been reported in the patients of obsessive compulsive disorder (OCD), bipolar disorder and amongst those with suicide attempts [47-50]. Toxoplasma gondii was recently found to encode a protein with high homology and showing similar catalytic properties to the tyrosine hydroxylases found in mammals [51]. This Toxoplasma gondii ortholog synthesizes L-DOPA, precursor to dopamine, as well as tyrosine,and has been demonstrated to result in increased dopamine levels associated with Toxoplasma gondii cysts in the rodent brain [46]. In a very recent study done of Toxoplasma infection in mice, it was found that the parasite infects the dentritic immune cells and manipulate them to secrete neurotransmitter called GABA a signal substance that, amongst other effects, inhibits the sensation of fear and anxiety. Disturbances of the GABA system are seen in people with depression, schizophrenia, bipolar diseases, anxiety syndrome and other mental diseases. Further investigations on the manipulative effects of Toxoplasma gondii infection on the GABA system will help to crack the toxoplasmosis and mental illness puzzle [52].

Study on the manipulation induced by latent Toxoplasma infection among the humans is still in its infancy. Experimental data from a study done on significantly higher number of human hosts is required to arrive at any concrete conclusion. Further investigation in this direction will certainly open up new avenues for behavioral manipulations induced by parasites in humans as a host.

3.4. The Curious Case of Candida Albicans Yeast

Candida albicans which is one of the most common infections among the sexually active women has evolved significantly [53].It has adapted to specially colonize vagina and these vaginal strains have also adapted to sexual transmission, specifically female-to-male transmission. The fungus can spread to the host's male partner by colonizing

his glans penis via vaginal intercourse or his oral cavity via cunnilingus [53, 54].This adaption of sexual transmissibility has been also supported with evidence from Genetic studies on change in allelic frequency for the same [54]. The most significant and highest level of adaptation achieved by this fungus is w.r.t to manipulation of sexual behavior in the host. Candida albicans infections have been linked with following five major aspects of human sexual behavior:

1). Early age of first intercourse,
2). Casual sex with previous unknown partners in the past month,
3). Vaginal sex during menstruation,
4). Oral sex [fellatio],
5). Receptive anal sex.

Candida albicans has also evolved to cross the blood brain barrier and colonize sites in human brain [55]. The most bizarre adaptation is the ability of this fungus to identify various regions of Brain and its capacity to adhere differently to different neuronal tissues. This recent adaptation of recognizing various neuronal tissues has been confirmed with autopsy of macaque brains.

In an ex vivo adhesion assay of primate Macacamulata in which tissues from frontal lobes and striatum [caudate, putamen, and portions of the globuspallidus were used, Candida albicans adhered to gray matter at about six times the level of its adhesion to white matter. The fungus was able to bind to different cell types within the cortex, basal ganglia, and white matter [56].Thus similar studies in case of the HPV infection might also help us to investigate manipulation of sexual behavior w.r.t to proximate mechanisms.

3.5. Colonization of Brain by HPV in Humans

HPV has been also successful in colonizing human brain as there is ample evidence on HPV as the causative agent for retinoblastoma in kids [57]. Colonization of the human brain in case of adults gives ample opportunity for hypothesized behavioral manipulations induced by virus directly or indirectly due to immune responses which may be of adaptive advantage to the virus. Adherence of the virus to specific areas like amygdala , hypothalamus , limbic system and other areas of brain that regulate Sexual behavior and similar traits might help to understand the level of adaptation by the virus.

4. Factors That May Contradict the Hypothesis

4.1. Sexual Signaling in Animals and Insects

Females in various species avoid males infected with parasites and parasite-free males are often found to advertise their status via different phenotypic traits which is a well-documented phenomenon in mainstream science [58]. This process selects for heritable resistance and reduces direct exposure of the female to parasites [59]. Parasites that coevolve with the host are likely to overcome this obstacle. Recently researchers [37] documented a case of parasitic manipulation of host mate choice. As per the report Toxoplasma gondii, a sexually transmitted infection of brown rats, enhances sexual at-

tractiveness of infected males [37]. Similarly insect virus Hz-2v alters mating behavior and pheromone production in Helicoverpazea moths. Virus-infected females were found to produce five to seven times more pheromone than control females and attracted twice as many males as did control females in flight tunnel experiments [60]. Thus under some evolutionary niches, parasites can indeed manipulate host sexual signaling to enhance their reproductive success.

4.2. Counter adaptations by the Host against Parasitic Manipulation

Reproduction is the crucible of Evolution even above survival. We all know because of short life span and high mutation rate the process of evolution is very rapid among the pathogens whereas it is not possible for us to keep up with their pace of evolution. In case of Humans it takes very intense selection pressures and many generations for evolution of a new trait. Parasites that are transmitted through sexual routes like that of HPV and HIV certainly have very high selection pressure to manipulate their host sexually because of very limited routes of transmission as if they fail to do so they will die with the host. Evolution of Persistence and benignity are another such trait shared by pathogens of STDs which gives them more chances of transmission during the entire lifetime of host and to enhance their reproductive success [60]. There is no such intense selection pressure on the Humans to come up with counter adaptive strategies as the advantage of sex is far higher than cost of the infection and anyhow the mortality associated with such infections are mainly in post-reproductive phase where selection pressure is too weak to help.

4.3. Presence of Other Infectious Agents within the Host

Hosts at a time may be infected with more than one parasite or multiple parasites. Manipulative strategy of one parasite might be dangerous for the reproductive success of other within the same host and in that case the counter manipulative response by the rest of the parasites may weaken the actual manipulation induced by sexually transmitted pathogens. Sometimes opposite can happen as the host might be infected with multiple STDs like HPV, HIV, and Hepatitis B etc. and in that case sexual behavior manipulation by one virus might actually give an adaptive advantage to others and thus can make it less costly affair for rest of them.

5. Adaptive Manipulation versus Accidental Effects

The observed manipulated behavior in the host may not always be directly induced by the parasite. Parasitic manipulation can be directly induced by the secretion of the bioactive compounds or they may be manifestation of the immune response of the host against the infection giving an evolutionary advantage to the parasite. Sometimes chemicals like Cytokines are secreted by the host as an immune response which does have a strong effect on various neuronal tissues leading to change in host behavior. Parasites can actually mimic this type of immune response by directly secreting cytokines and induce similar change in host behavior to get an evolutionary advantage. Different parasites may induce different immune responses which can elicit different

behavior in the host [61, 62].

Several examples of pathogens affecting the proximate mechanisms were reported that mediate the expression of social behaviors in vertebrates (aggressive, reproductive and parental behaviors), in ways that may increase parasitic transmission [63].

6. Conclusion

Evolutionary or Darwinian medicine, a nascent research area in medicine can significantly contribute in understanding of the sexually transmitted diseases. Evolutionary methods can help to analyze host-pathogen co-evolution that shapes extreme traits whose costs can be substantial to the host. It is equally important to determine the exact proximate causes of host behavior manipulations for better understanding of sexually transmitted diseases and their treatment. It is also necessary to apply interdisciplinary approach to answer the challenging questions offered by host manipulation studies. Knowledge derived from such research may contribute to public health and may help us to take a step closer in the constant evolutionary battle with the pathogen. If pathogens like HPV, HIV, hepatitis B and Candida albicans affects sex hormone levels; this might be the proximate means of behavior manipulation. It doesn't matter whether this effect began accidentally. This is how evolution works. An accidental effect is seized by natural selection and then refined to make it work better. The advantages of understanding diseases from the evolutionary perspective are enormous and this will help further theory of Evolution to achieve its true worth in Medical Science for better understanding of diseases and their treatment.

Conflict of Interest

The author has no conflicts of interest to declare.

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