Varying Presentations of Illnesses in Genetically Related Species: Sialic Acid Hypothesis

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A philosophical question that has bedevilled many students of medicine, myself included, is whether there are any illnesses that are truly human specific - and if so, why are the other animals immune. Ethology has been able to invade the anthropological domain not just in the field of behavioural sciences but also in the biological sciences. It is therefore all the more puzzling why, apart from a few exceptions, many of the major human killers have not been researched to determine whether they have an equivalence in the non-human mammals. The query has assumed special significance now that we are dealing with COVID-19 whose provenance is attributable to an animal virus that has mutated into a human virus and is creating international havoc even as I pen this column. We do not know much about the effect of this virus in the bats; we have not studied whether their physiology has been affected in similar manner to the humans. During the phase of this pandemic, we noticed how this virus was transmitted to minks in Denmark only to be transferred back to humans in a mutated form. Some leading biomedical researchers, notably Varki and Ayala, have provided us interesting insights. As I pen this column, a number of great apes have been found to be infected with COVID-19 - the first such instance in a species that has over 97 percent similarity to the humans. They tend to believe that Sialic Acid (n-acetylneuraminic acid) may have a role to play in determining the different presentations of illnesses between human and the other primates whose genetic make-up would otherwise be very similar.

Our closest relatives in the animal kingdom are the great apes. Unsurprisingly, a number of studies have been conducted in the great apes to determine whether certain diseases hitherto considered human specific could be induced in the great apes. The snag, of course, is that these studies were conducted on the apes when they were in total captivity. The studies at the National Institutes of Health were conducted when apes, despite being in captivity, were being provided veterinary attention. The artificial conditions created in the experimental conditions were different to the animal's natural habitat. But in most cases, they were able to provide clues whether a particular human illness could also be reproduced in animals.

Ace biomedical researcher, Nissi Varki, in her ground-breaking research discovered that while heart ailments were common in both humans and chimpanzees, the pathological process was entirely different. A human heart on account of coronary blockage could result in fatal myocardial infarction. In the chimpanzees who developed heart failure, the cause happened to be interstitial myocardial fibrosis. [1]

The two salient queries that emerge from this study are:

1. Humans hardly ever show fibrotic heart disease that is so common in all our relatives within the animal kingdom viz orangutans, bonobos, gorillas and of course chimpanzees; and
2. These animals rarely exhibit myocardial infarction that is so very prevalent in the human beings

Varki and her colleagues then went about on her funded project [2] precisely to try to find answers to these important questions. They decided to study two human diseases i.e. myocardial infarction and malignant malaria. On literature survey, they were intrigued to discover that certain researchers nearly a hundred years ago had actually performed a two-way blood transfusion between chimpanzees and human beings who were either infected or free of malaria. Despite follow up, there was no evidence at all of cross infection. The parasites involved in humans and chimpanzees, although similar in appearance, were actually quite different and behaved in a very different manner.

Francisco Ayala and colleagues in their classic study

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[3] had already shown that Plasmodium falciparum, the organism responsible for malignant malaria actually arose from Plasmodium reichenowi by one transfer from a superb ape. There are several kinds of ape malaria that are mild and prevalent throughout Africa. At an unknown stage, humans escaped primarily because of a change within the surface sialic acid molecule. Unfortunately, one among them finally worked out the bind to the sialic prominent in us, which is now why we suffer from Plasmodium falciparum malaria.

Enteric fever was another illness that was generally believed to be human specific. Many studies have demonstrated that enormous doses of the Salmonella bacillus were unable to induce typhoid in apes. Jorge Galán discovered that the typhoid toxin, which is that the soluble molecule that basically mediates the severe symptoms of typhoid, cannot bind to the chimpanzee cell surface but could easily bind to the human cell surface (sialic acid difference between the species).[4]

Cholera is a serious killer in humans. Robert Koch way back in 1884 observed that "... although these experiments were constantly repeated with material from fresh cholera cases, our mice remained healthy. We then made experiments on monkeys, cats, poultry, dogs and various other animals ... but we were never able to reach anything in animals almost just like the cholera process." Vibrio cholerae doesn't induce diarrhoea in adult animals other than humans.[5]

There are many other diseases which can be termed human-specific. Another set of diseases during which various bacteria perform molecular mimicry in which bacterial capsular polysaccharides mimic common motifs on sialoglycans of mammalian cells. Till now, no captive great apes have reported carcinomas of the oesophagus, lung, stomach, pancreas, colon, uterus, ovary, or prostate. Several thousand great apes are living in captivity well into their fifties and sometimes into their sixties. Varki and colleagues after an extensive study concluded that "while relative carcinoma risk could also be a possible difference between humans and chimpanzees (and possibly other great apes), a more systematic survey of obtainable data is required for validation of this claim".[1]

Interestingly great apes do not seem to suffer from asthma, a very common disease altogether human populations. A very erudite paper [6] concluded that this case that was studied was "remarkable because there's a paucity of reports of present allergic airway disorders in nonhuman primates."

On basis of her studies, Varki *et al* [1] was able to draw the following inferences:

- The disease profiles of humans and chimpanzees are rather different even when it comes to illnesses supposedly from the same offending organism or a consequence of the same pathophysiological abberration.
- Chimpanzees present inexact models of the various human diseases.
- Humans are likely to present equally inexact models for the various chimpanzee diseases.

Effectively, on the basis of evidence at hand, it would be possible to state that there indeed are certain diseases that are human specific and one of the reasons could be the sialic acid profile which is very different between the humans and their closest relatives in the animal kingdom. We have hitherto placed an excessive reliance on animal studies in human medicine which would not be able to tell us much at least in the human specific illnesses.

But this is an area ripe for research. The entire planet is battling COVID-19 which has been supposedly transferred to humans from bats and mink to human transmission has also been observed in Denmark. In order to gain a proper understanding of the microorganism we are battling now-and for future reference, it would be important to understand the reasons why certain diseases remain human specific and what makes them so.

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