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EDITORIAL

Hepatitis C in Punjab—Peeping into Pandora's box!

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An array of non-communicable diseases as well as chronic infections related to ongoing economic and lifestyle swings on the one hand, and a legacy of "traditional" communicable diseases on the other, characterize the emerging disease burden scenario of the developing and transitional economies of the world [1]. India is in the middle of huge socio-economic and demographic swings, and the pattern of its health care challenges is also changing [2]. The liver, as an organ, presents the perfect interface for this disease burden "spectral drift". The infection—lifestyle interplay in etiology, disease biology and outcome are all too evident in the case of chronic liver diseases - hepatitis C virus (HCV) representing the "infection port", while alcoholism and metabolic syndrome (MS) related nonalcoholic fatty liver disease (NAFLD) highlight the contribution of "lifestyle" in this evolving pattern [3]. Public health planning, prioritization and allocation of resources in India need to be cognizant of all these features of liver disease burden to be futuristic and useful. While disease burden includes a range of biological (etiologies), clinical outcome (morbidity, mortality), system stressors (health care utilization) and economic factors that are relevant in planning preventive strategies, the most simple, objective and useful measure of burden is an estimate of prevalence of an etiological agent like HCV and HBV in the population [4, 5].

In chronic infections like that caused by HCV, prevalence studies are important epidemiological "eye openers" as they bring into focus the magnitude of the current health care burden due to it [6, 7]. Over and above, they provide the frame for downstream descriptive and analytical studies as well as provision of well phenotyped cohorts of infected individuals for precise delineation of the natural history of infection and disease at a later time point. Widespread geographical and ethnic differences in the prevalence of HCV are well known globally [8]. Such variations in prevalence provide insight into the risk factors and mode of transmission of the virus in the population in context and can guide targeted interventions. Thus in Egypt, the country with highest HCV prevalence globally, elegant epidemiological studies demonstrating a close association between a nationwide campaign against schistosomiasis by parenteral injections of tartar emetic by health workers and prevalence of HCV in the general population led to a country wide campaign against injection abuse [9, 10]. India, with its rich population diversity, has tremendous loco-regional differences in prevalence of HCV as well as of HBV [11, 12]. Thus, while isolated ethnic groups have been demonstrated to have very high HCV and HBV prevalence, the overall reported HCV prevalence in the population has been around 1 %.

Sood et al. in a population based survey from Punjab, now report a very high (5.2 %) seroprevalence of HCV infection, with highest prevalence in the 40–60 years age group and a significant clustering of infection within families [13]. A fairly low HCV RNA positivity and a uniform sex distribution of prevalence are some of the relatively intriguing features of the current data, as compared to those available from India and worldwide (more than 60 % seropositives have active infection and a male:female ratio >1). The large number of samples (more than 5,000) assayed for HCV seroprevalence is the most important strength of the current study, while a more robust epidemiological design, particularly in terms of sampling, strategy for population inclusion, risk factor questionnaire development and administration, precision in statistical analysis (only univariate

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analysis has been done) would have provided a more detailed analytical insight into the HCV population data warehouse that this study has generated. Nevertheless, the lessons that the study provide are too pressing from a public health view point. The group need to be applauded for this attempt to take the lid off the black box lying in the HCV capital of India and provide objective dimensions to the perception and notion that HCV prevalence is towering in the country's north-west corridors.

Some of the paradoxes of the data presented are again too striking to be ignored from a biological viewpoint. While females fare well with HCV—the prevalence of infection is lower, the progression of liver fibrosis slower and therapy responses better putatively due to estrogenic influences—the current study found equal prevalence of HCV in both the sexes [14]. An over inclusion of females in the current study compared to that of the background population of Ludhiana (sex ratio 1,125 vs. 869) seems to be responsible for this. However, the low RNA positivity remains unexplained.

However, the most interesting biological research question is why it is that Punjab has such high prevalence of HCV. This issue assumes greater importance when we note that HCV prevalence in Punjab across the border is also high whereas it is much less amongst other population groups and provinces in Pakistan [15].

Is it linked with ethnicity? This is the natural first question the way Punjabis carry the virus more than others do in both India and Pakistan. Racial differences in HCV biology are well described and now host genetic factors are providing clues to that [16]. Single nucleotide polymorphisms (SNPs) near the IL28 B loci on chromosome 19 has been shown to predict response to therapy and spontaneous clearance of infection after acute exposure in HCV infection [17, 18]. Presence of a C instead of T at rs 12979860 (one of the SNPs that has been linked to HCV outcomes) of IL28 B loci correlates with a high initial viremia after exposure, high expression of interferon sensitive genes (ISG) in the liver and a higher probability of spontaneous clearance (and therefore low persistence rates) after exposure. The ethnic differences in HCV therapy response in reported studies could also be explained by differences in IL28 B background allele frequency in the population in context. All these raise the tempting question in Indian context—are host genetic factors the primary driver of the Punjab HCV enigma? We hope the answer will come soon in the Indian population.

It may be mentioned here that host genetic factors should not be seen in isolation in analysis of complex traits and biological phenomena, particularly those due to infection. HCV is a virus with tremendous genetic drift and exists as a quassispecies. Viral kinetics and evolution of HCV sequences are under tremendous selection pressures—those due to immune response (positive selection) and due to intrinsic viral fitness (negative selection). Evolutionary rates in the hypervariable region 1 (HVR1) of the E2 gene of HCV has been shown to discriminate between self resolvers and persisters after HCV exposure and acute infection [18–20]. Thus, host—virus interactions, genetic and immunological, are likely to be important here too, instead of a skewed view of host genetics being the sole determinant of outcome after exposure.

The crucial first step after this preliminary important survey will be to carry out a rigorous epidemiological study on HCV infection in Punjab. Punjab and Egypt are related in history—Indus valley civilization and that of Egypt did have potential cross talks in trade and culture—both existing around the same time. HCV has the potential to reunite the two, now in pain and disease. Here again one needs to learn from the other. We need to generate sound epidemiological data as Egypt did, including surveillance systems to lead our planning of HCV control [21, 22]. Health research in a country is guided by policy ambience [23]. Unfortunately, population based epidemiology is not accorded high enough priority in Indian science. A shift in thoughts and prejudices in the mindset of our health planners, science research agencies and, above all, medical researchers is necessary and that is visible in the current study.

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