Better Outcome of Schizophrenia in India: A Natural Selection Against Severe Forms?

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Regional variations are observed in outcome of schizophrenia, but reasons remain unclear. Outcome of schizophrenia is reported to be better in India. In this report based on census data, we highlight substantially greater mortality observed among the mentally ill than among the general population during famines in India in the 19th century. A possible selection against the most severe forms of schizophrenia could account for greater occurrence of better-outcome phenotypes. Population histories and environmental influences, including epigenetics, need to be considered to further investigate differences between schizophrenia phenotypes.

Key words: famine/phenotype/epigenetics

Introduction

Two follow-up studies conducted by the World Health Organization, viz, International Pilot Study of Schizophrenia1 and Determinants of Outcome of Severe Mental Disorders,2 showed that the outcome of schizophrenia is better in Indian centers. A recent article questioning the axiom of better outcome of schizophrenia in the developing countries also noted that this finding is true specifically in terms of symptomatic and functional outcome.3 Isaac et al,4 in their review of outcome of schizophrenia across low–middle income countries (majority being from Indian centers), note that explanations for this phenomenon are far from being clear. Several hypotheses, eg, early death of bad-outcome cases, different genetic background, greater societal tolerance and better support provided by the families and the community, and less competition in preindustrial and predominantly rural societies have been proposed,5 but reasons for this variation remain poorly understood. Sociodemographic and clinical variables predict only about 25% of variance in long-term outcome of schizophrenia,6 and other factors thus need to be considered. Schizophrenia may have become milder over the past 2 centuries, and natural selection against the severe forms of schizophrenia has been proposed to be one of the factors that could be responsible for this.7 Analysis of the census records of southern India, including Mysore Kingdom and Madras Presidency, for the years 1871–1901 suggests that such a mechanism could be particularly true in India and suggests some contribution to the relatively better outcome of schizophrenia.

Census Data on Famines in India

We compared the records of the Mysore and Madras regions in the census reports of 18718,9 and 1881.10,11 Census records of Mysore state reveal that there was a decrease in the number of mentally ill by almost 75% in 1881, when compared with the numbers in 1871. This was attributed to the severe famine of 1878–1879, and proportionately, more mentally ill died than the general population (about 20% of the general population died and returned to levels of 1871 by the 1891 census). The Superintendent, Lunatic Asylum, Bangalore, pointed out in his annual reports that the mentally ill were often abandoned, and mainly those who were in contact with the asylum (less than 5% of the total number of those with severe mental illness) survived.12,13 As Mr McIver, one of the chief officers in the Mysore Kingdom, noted “the famine of 1876-78...certainly killed off an abnormal proportion of those of unsound mind. It is clear from the figures that these poor people suffered terribly.”10 In the Madras region, in 1871, 14 107 persons were returned as insane against 10 098 in 1881. Of this decrease, more than three-fourths occurred in areas containing less than two-fifths of the population, which were the famine districts. The decrease of the insane in the famine districts was 47.52%, in the nonfamine districts 10.12% per cent. The final census reports of 189113 and 190114 document the continuing impact of these famines, as evinced by the smaller numbers of mentally ill in Mysore and Madras regions. Similar changes were also observed in response to

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food scarcity in other regions. In the case of the Bombay Presidency (the whole of western India), the number of mentally ill showed a decline greater by 50 per cent, in the 1901 enumeration, as compared with 1891, attributed, by the commentator, as due to a “better diagnosis, but the main reason seems to be that the insane suffered far more than the general population in the years of scarcity of food.” Gender ratios were equal through these periods in Mysore and Madras regions. Equal proportion of men and women had died across all regions during the famines.

**Discussion**

India has faced famines at regular intervals, and the available documentation provides some detail during the Mughal and British periods. The emphasis on feeding the urban populations under the Mughals and the delayed responses to the widespread famines between 1750 and 1950 under Colonial rule could perhaps have resulted in similar dynamics being played out in every famine. It is thus likely that a considerably large proportion of the most severely ill would have died in each cycle. The average life expectancy in India in the 19th century was less than 25 years, and those with the early onset and most severe outcomes were thus the ones most likely to have been affected by the famine. Those with milder forms of the disease would thus have survived and procreated. One could conceive that such a phenomenon could lead to the next generation having lesser proportion of patients with severe illness. We propose that this natural selection against severe forms of schizophrenia could explain, in part, the heterogeneity observed in outcome of schizophrenia across the globe.

A couple of caveats need consideration to put the census findings in perspective. Firstly, the census archives provide data on “mental illness.” It is difficult to say how the diagnoses made in this pre-Kraepelinian era relate to the current classifications. The diagnostic nomenclature used during that period in India was identical to that used in the Great Britain at that period. The diagnoses included “Mania Longa,” “Mania Acuta,” “Melancholia,” “Monomania,” “Mania Episodica,” and “Dementia Acuta.” The proposed hypothesis should be considered in the background of lack of clarity about their relationship to the contemporary concept of schizophrenia and nonavailability of specific mortality data across these diagnostic entities. However, it is reasonable to believe that the “mentally ill” at that time had psychosis of some sort, and a substantial proportion of them had what could now be considered as schizophrenia.

Secondly, in other developing countries that have faced repeated famines (eg, China), the outcome of schizophrenia appears to be poor. The impact of famines on mortality may be mediated by sociocultural and other biological factors. It is not clear if there was a differential impact of the famines on the mortality of severely mentally ill vs that of the general population. Studies specifically examining the impact of famines on mortality of schizophrenia patients vis-à-vis general population in China may throw better light on this hypothesis.

Early onset and male gender have been known to be associated with poor-outcome schizophrenia. It has been consistently documented that cohorts of first-episode schizophrenia in India are characterized by underrepresentation of youngest onset males, which contributes to the lack of sex difference in age at onset in these cohorts. This observation is in keeping with the hypothesis that those with poor-outcome schizophrenia may have been eliminated by natural selection. Famines have been implicated in causing increase in the incidence of schizophrenia. However, no data are available about the incidence of schizophrenia following these famines, in these regions of India.

The impact of these environmental events, and possible selection pressure, on the epidemiology of complex diseases is still a matter for speculation. Repeated cycles of famine are thought to have contributed to the increased prevalence of diabetes in the south Asian population and a “thrifty gene” hypothesis proposed wherein particular genetic variations (PPARG/Ala12) are thought to confer susceptibility/protection against diabetes. Selection pressure and allele age have been incorporated into models to explain the ethnic differences in the prevalence of diabetes, while more recent data suggest that gene-gene interactions (rather than variations in PPARG alone) could be responsible for the genetic observations. In addition, a number of epigenetic influences, including environmental stresses, may alter gene expression in subsequent generations and thus influence disease manifestation. Selection for both nutritional and neural genes is an ongoing process. Variations in copy number of amy-lase genes (that could influence susceptibility to diarrhea and malnutrition, likely during famine) seem to differ across populations depending upon their diet, and co-evolution of genes in immune responses could explain patterns of variation, as well as the prevalence of autoimmune and infective diseases. The risks of transmission of susceptibility to develop severe mental illness are likely to be as complex as those for diabetes, autoimmune disorders, or resistance to infection. Awareness of these past environmental bottlenecks and population histories may help us plan our genetic research better and also provide another avenue of inquiry to explain the differences in disease characteristics between populations.

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References

1. WHO 1979 Schizophrenia: An International Follow-up Study Chichester, UK: John Wiley and Sons.