RECENT ADVANCES IN GENETIC RESEARCH IN LEPROSY

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There is now evidence from studies of population difference, genetic markers and twins that host genetics play a role in determining the susceptibility and/or type of response to infection with *M. leprae*[1].

A host, who appears to have no demonstrable T-lymphocytes capable of mounting an effective cellular immunity against lepra bacillus, is the likely candidate for developing lepromatous form of leprosy, following infection. This immuno-deficiency, fundamental to the lepromatous patients is, however, highly specific, in vitro tests for cellular immune response to other antigens being usually unimpaired otherwise[2]. Specific nature of this defect, indeed, appears to suggest that it pre-exists in the host as a genetically determined factor[3,4].

One of the most growing points of leprosy research of the day is evaluation of the role of genetic defects which presumably presage the development of lepromatous leprosy in a host. There has recently been considerable progress in research in this area, the important aspects of which are reviewed in this paper.

Pedigree Analysis

Human populations vary in frequency of particular genes within them. Genes governing the pathogenesis of leprosy were assumed to show similar variation in different populations, in view of the fact that the entire sibship was rarely affected in a multiple case family and conjugal leprosy occurred rather infrequently[5,6]. Limitation to spread of the disease within families possibly indicated segregation of the genes concerned[7]. Penetrance of the gene, being considerably influenced by the environmental factors like opportunity for contact with an open case, is expected to vary in populations. Indeed, Spickett[8,9] postulated that distribution of different types of leprosy in the affected individuals was governed multifactorially.

Twin Studies

In case, susceptibility to lepromatous form of the disease is genetically determined, a higher degree of concordance for the disease type would be seen for MZ, rather than the DZ twins. Higher rate of concordance for the disease type for MZ, compared to that for DZ twins, in the twin studies of Spickett[7], Ali and Ramanujam[10,11], and Chakravartti and Vogel[12] tends to suggest existence of a genetic background.

However, the most widely studied series of Chakravartti and Vogel[12] had 5 (13.5%) MZ twins who were concordant for leprosy but showed discordance for the disease type. In other words, one of the co-twins had tuberculoid although the other was afflicted with lepromatous leprosy, notwithstanding the fact that he had the genetic capacity to express a sufficient degree of cellular

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immune response to *M. leprae*[13]. Besides, twin studies are likely to have a bias in favour of the concordant pairs, since the twin samples are often collected from leprosy hospitals or clinics where only the concordant pairs are likely to be known.

A B O, Rh Blood Groups

Possibility of an association between blood groups and leprosy has often been investigated[14,15,16]. Although a significant association between O-group and tuberculoid rather than the lepromatous leprosy, was detected in the series of Yankah[17], other studies failed to confirm this. Therefore, there appears to be no reasonable ground to associate leprosy or its different forms with A B O and Rh blood groups.

Australia Antigen and Leprosy

Australia antigen (HB Ag) has been found to be significantly associated with lepromatous leprosy, rather than tuberculoid type or the healthy controls[18,19,20]. HB-Ag has been thought to be inherited by simple autosomal recessive gene. Individuals homozygous for the gene, may have detectable HB-Ag in their sera and appear to be more susceptible to "HB-Ag affinity group of diseases" which includes lepromatous leprosy.

HLA System and Leprosy Ir Gene

This has, probably, been the most widely explored area of genetic research in leprosy in recent times. The HLA complex consists of a number of loci located on chromosome[6]. Four of the loci (A, B, C and D) control the surface antigens of nucleated cells as well as some immune response, while others control some complement factors.

De-Vries[21] observed a significant deviation of antigen types from random HLA haplotype segregation in families where the sibs were afflicted with same type of the disease. The sibs in these families were found to share the parental HLA haplotype more often than the random expectation. In a similar study[22], observations were suggestive of presence of a genetic determinant, linked to the major HLA locus, which is probably recessive and affects susceptibility to tuberculoid leprosy in humans.

Izumi et al[23], in a study of 45 patients from 21 families having leprosy in more than 2 generations, observed a strikingly high frequency of linkage for HLA-A9 and B-7, contrary to that found in healthy Japanese population. Moreover, antigen frequency of B-12 and B-35 was significantly low in the study group. Thus, a linkage disequilibrium was apparent in this study and the observation was suggestive of existence of a genetically determined immunological background for pathogenesis of leprosy.

Although in a study in India[24], an association was observed between HLA-DR W2 and tuberculoid leprosy, Rea et al[25] in Mexico found no such association between leprosy and HLA antigens. Again, in an attempt to evaluate the influence of HLA-D identity, Stoner and Touw[26] found no evidence for a deficient in vitro response of HLA-D identical healthy sibs of lepromatous patients to *M. leprae* in LTT. This, indeed, does not appear to support the hypothesis that lepromatous patients carry any HLA linked genetically determined immuno-deficiency as far as leprosy is concerned.

Lepromin Reactivity and Susceptibility to Leprosy

Beiguelman's[27] observation that 30.9% of the children of 24 lepromatous couples showed a highly positive late lepromin reaction did not support the hypothesis that an autosomal gene pair was responsible for lepromin reactivity. Mitsuda (lepromin) reaction pattern of 127 healthy twin pairs of either sex, living in a leprosy endemic area,

revealed no significant difference between MZ and DZ twins[28]. This observation, therefore, does not indicate that lepromin reactivity is genetically determined.

Innate immunodeficiency has been thought to underlie the lepromin negativity in lepromatous patients[29]. In a prospective study in India, 26.9% of the lepromin negative contacts eventually developed leprosy, mostly lepromin positive contacts, none of whom indeed had lepromatous form of the disease[30].

Family Studies

If genetic factors played any significant role in determining the type of leprosy, within multiple case families there should be a tendency for clustering of similar type of the disease, rather than the random expectation pattern in general population. Keeping this in view, Horton and Povey[31] surveyed 84 multiple case families and found concordance rate for the disease type in parent/child and sib/sib relationship to be 40% and 45% respectively, while the overall concordance was 42%.

In their study of 98 multiple case families, Guha et al[32] observed a disease type concordance rate of 26.7% and 65.4% in parent/child and sib/sib relationship respectively. However, the overall concordance rate was 36.6% in this series. A significantly high concordance rate for sib/sib relationship in this study was attributed to the fact that the sibs shared a common environment, unlike their parents who might have been in a different environment at the time of contracting the disease.

Therefore, no significant concordance for the disease type among the first degree relatives was observed in these studies, compared to random distribution pattern in general population.

Again, White et al[33] in their study of a group of 20,990 children in Uganda, over a period of 8 years, recognised no important genetic influence on the incidence of leprosy, once an allowance had been made for the extent of physical contact between the index cases and at risk groups. Therefore, observations in this study and in that of Guha et al[32] were not different.

DNA Repair Mutants and Leprosy

Recent investigations on DNA repair mutants in human disease revealed that some heterozygotes were detectable at a high frequency and many of the homozygous patients suffering from some of the chronic infectious diseases had selective immunological dysfunctions. There were indications that the heterozygotes might also have impaired immunological capacity and identification of them might have important implications in studies aimed at detecting predisposing immunological factors in chronic infectious diseases, including leprosy[34].

B-Cell Alloantigen and Susceptibility to Lepromatous Leprosy

Screening a large group (10,000) of multiparous sera against peripheral blood mononuclear cell sub-population of lepromatous leprosy patients, Patarroyo et al[35] recognised the existence of an alloantigen in a particular serum (MP-01833) that reacted with 60% lepromatous leprosy patients and 16% of the normal controls. It, however, did not show any reactivity with tuberculoid leprosy or other diseases like tuberculosis, rheumatic fever or SLE. This, in the opinion of the authors, shows high selectivity for a genetic marker associated with susceptibility to lepromatous leprosy, which reveals an autosomal dominant segregation pattern expressed on B-cell subpopulations and on a minor T-cell population.

Comments

Genetic analysis of leprosy should clearly identify at least three subsequent factors : (a) evidence for genetic determination of susceptibility to the disease, and (b) to its clinical types, (c) genetic factor or factors involved in the disease susceptibility.

Clustering of leprosy patients within families has been interpreted by some authors as a reflection of genetic influence on susceptibility to the disease of its types[8,9,10]. However, other associated epidemiological factors like close "intrafamilial contact" may as well be equally or even more important in this respect. Most of the published reports have taken into consideration only one of these factors, i. e., genetic or contact. However, the recently published study of White et al[33] is especially important in this context, for it has made an allowance for the extent of physical contact between the index cases and "at risk groups". No influence of genetic relationship, indeed, has been recognised in this study, as far as susceptibility to leprosy is concerned.

Notwithstanding the fact that an association between certain antigens of HLA system and some diseases has been clearly documented, this has not been thoroughly explained[35]. Of the many studies conducted to identify by an association between HLA-A or D loci and leprosy or its various clinical forms, only a few revealed such association in respect of HLA-A or B alloantigens[21,22,23]. Again, while some of the studies[24] recognised a significant association between HLA-DR and tuberculoid leprosy, none showed any linkage with the lepromatous type. Findings of Stoner and Touw[26], indeed, give a new twist to the hypothesis of many authors, in that no positive relationship between HLA system and genetic susceptibility to the disease was apparent in this study.

Although a recent and rather an extensive twin study[12] recognised the influence of a genetic background, 5 MZ twins who were concordant for leprosy showed discordance for the disease type, which appeared to suggest that one of the co-twins developed lepromatous lepsosy even though he had genetic capacity to mount an effective cellular immune response to M, leprae. Further more, in a twin study, it is often difficult to avoid a bias in favour of concordant MZ twins, since an excess of them are likely to be reported.

Some of the other studies, like presence of Australia antigen[18,19,20], lepromin reactivity[30], DNA repair mutants and leprosy, and identification of B-cell alloantigen[35] although tend to indicate that host genetics play a role in determining susceptibility to the disease or its types, the mechanism and extent of this remain unknown. These areas of research need further confirmation on much larger groups and on different populations.

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