Evidence for Infectious Component of Hodgkin’s Disease and Related Considerations

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Summary

The four epidemiological approaches used to evaluate the hypothesis that Hodgkin's disease might have an infectious component are reviewed. The limitations of each approach are summarized and some related questions are raised. The emerging picture for Hodgkin's disease is that a variety of factors, both environmental and genetic, might be important in the etiology of this disorder.

The only etiological hypothesis for Hodgkin's disease that has been intensively pursued to date relates to its possible infectious nature. Recently, several investigators have evaluated the epidemiological (1, 29) and immunological characteristics of this disorder to determine whether they are consistent with this hypothesis. For example, Order and Hellman (21) have suggested that the cellular surface of thymus-derived lymphocytes undergoes some antigenic alteration during viral infection. Hodgkin's disease might then be viewed as the result of a chronic immune reaction, characterized by an eventual depletion of T-cells, caused by viral infection of these cells and normal T-cells interacting against antigenically altered ones. This hypothesis gains additional plausibility by the fact that it might explain the heterogeneity of cells (i.e., lymphocytes, plasma cells, and eosinophils) found in typical Hodgkin's disease lesions, the axial lymphatic distribution of Hodgkin's disease, and the occasional presence of anergy. It should also be mentioned that this theory is consistent with the graft-versus-host hypothesis for this disease proposed by Kaplan and Smithers more than a decade ago. It is the purpose of this report to summarize the epidemiological evidence suggesting that Hodgkin's disease might be infectious in nature. Consideration will also be given to the limitations of epidemiology in evaluating this matter and some related questions.

To date, 4 different epidemiological approaches have been taken to evaluate the possibility that Hodgkin's disease might have an infectious component: (a) the possibility that prior tonsillectomy might predispose to Hodgkin's disease, (b) studies of case groupings, (c) occupational mortality studies, and (d) family studies of this disorder.

Tonsillectomy and Hodgkin's Disease

The concept that prior tonsillectomy might place a young individual (40 years of age or less) at increased risk for Hodgkin's disease can be considered an extension of the viral hypothesis for this disorder. This issue has now been the subject of several studies (11, 14, 20, 33), and considering the possibility that socioeconomic status might be an important factor in the incidence of both tonsillectomy and Hodgkin's disease in the United States, it is generally agreed that the sibs of cases represent the best comparison group. As indicated in Table 1, which summarizes the risk ratios found in 4 studies that have used sibling controls, there does appear to be an overall positive association between Hodgkin's disease and prior tonsillectomy. However, a wide range of risks have been observed (1.2 to 3.6), and it will be important for future studies to consider whether this might be due in part to variations in study design. For example, it is well established that the selection of cases from a single medical facility could introduce a bias arising from selective factors that lead patients to that particular institution. This is especially important when sib controls are used. Sibs are likely to have similar tonsillectomy histories, and if they reside in an area serviced by a hospital where this operation is readily performed, it might be exceedingly difficult to detect any difference between cases and their sib controls without studying large numbers. Another bias can result when a study excludes dead cases.

Some attention should also be given the great heterogeneity that exists within the lymphatic system (2). Table 2 indicates the age periods during which various lymphatic organs attain maximum size and then regress. It must be realized that this listing oversimplifies the changes that occur, for a significant variability also exists within the various organ groups. For example, the structure of lymph nodes varies in different parts of the body, and glands within certain anatomic groups show different stages of development (8). This is particularly true when superficial nodes (e.g., inguinal) are compared with deeper nodes (e.g., deep cervical). If we knew the mechanisms for and the immunological consequences of these changes that occur with age, our understanding of the various lymphomas and their age incidence patterns might be greatly enhanced. An initial step in this direction has been taken by Miller (19), who suggested that tonsillar involution might be associated with the sharp increase in Hodgkin's disease mortality rates after the 11th year of age.

Hodgkin's Disease Groupings

Since the initial report of several linked cases of Hodgkin's disease occurring among a particular group of students who attended the same high school (32), several
additional groupings have been described (9, 15, 27). While it is clear that these case aggregates do not represent formal proof of the infectious hypothesis in Hodgkin's disease, to dismiss them without further consideration is to deny the possibility that they may be biologically relevant. Since any fact might be important, these groupings must be analyzed for characteristics that they might have in common, and consideration should then be given to the consistency of these observations with established infectious disease concepts. For example, most Hodgkin's disease cases in the groupings studied could not be linked directly to other cases. This might well be expected if some viral agent involved in the etiology of this disorder. Two intimately related features of many viral disorders are survival of the parasite, which is contingent on a high percentage of infections being mild and nonfatal, and the greater importance of individuals with mild illnesses and healthy carriers in transmission than fully developed cases. A microbial agent was involved in the etiology of this disorder. Two intimately related features of many viral disorders are survival of the parasite, which is contingent on a high percentage of infections being mild and nonfatal, and the greater importance of individuals with mild illnesses and healthy carriers in transmission than fully developed cases. A microbial agent with neither of these features is greatly limited in its capacity to disseminate and therefore to survive. What this might suggest to the virologist and immunologist is that familial and social contacts of Hodgkin's disease patients might be worthy of detailed study. To the epidemiologist, it should raise the possibility of a carrier state, which must be considered in designing objective studies. Many of the other features that the Hodgkin's groupings have in common have recently been summarized elsewhere (30) and will not be dealt with here. However, another potentially important characteristic is the close nature of the personal contacts prior to the onset of disease among linked cases (15, 27, 30). Again we must ask whether this apparent feature is observed in other diseases of known infectious etiology. A study that compared tuberculous children born of tuberculous parents with children who escaped tuberculosis in such families (25) concluded: "the disturbing thing, and the thing which demonstrates that much further work must be done on the problem, is that in every case the close contact rate is higher for the tuberculous offspring than it is for the non-tuberculous offspring."

There is a definite need for additional studies of Hodgkin's disease groupings. Admittedly, this approach will produce no definitive answers, but it may well provide some important insights, just as single case reports have done in the past. A large body of evidence derived from regional, national, and international studies suggests that environmental factors are important in Hodgkin's disease (29) and that susceptibility varies with age, sex, and the standard of living (6). If we are to refine these observations and dissect the vague term, "environmental," studies on the community level will be required. In fact the incidence of Hodgkin's disease among older adults is related to the pattern of incidence in younger life (6), we must then ask how these 2 groups interrelate. Could this observation, which is based on data from several different countries, be a reflection of the predominant patterns of apparent transmission seen in many of the Hodgkin's disease groupings, namely, young to old and young to young (32)? Objective epidemiological studies will be required for answers, but case aggregates are a major source of questions. A ready example of this is the fact that the index-secondary case approach for evaluating the transmission hypothesis was derived primarily from analysis of the apparent features of Hodgkin's disease groupings. Thus, it was hypothesized that in the 777 public schools of all types in Nassau-Suffolk counties, institutions with index cases (students or teachers) during the years 1960 through 1970 would have more than the expected number of secondary cases (students or teachers) during the study period (34). A modification of this hypothesis could be that public high schools with cases present during the years 1960 through 1964 would be more likely to have additional cases during the years 1965 through 1969 than control high schools without cases during the earlier period (2-time-period approach). The results obtained from both approaches were consistent with the possibility that transmission might be an important component in Hodgkin's disease under certain circumstances.

The major criticism of this study deals with the completeness of case ascertainment (22). Thus, the average annual incidence rate for Hodgkin's disease in the study area was 1.9/100,000 population, which is lower than the average national rate. It seems clear, however, that rates for this disorder do vary both on the international level (16) and regionally within the United States (5). Furthermore, while under ascertainment of cases could undoubtedly effect the

Table 1
Summary of the risk ratios of Hodgkin's disease associated with tonsillectomy in studies using sib controls

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newell et al. (20)</td>
<td>1.2</td>
</tr>
<tr>
<td>Johnson et al. (14); Pike et al. (23)</td>
<td>2.0</td>
</tr>
<tr>
<td>Vianna et al. (33)</td>
<td>3.6</td>
</tr>
<tr>
<td>Gutensohn et al. (11)</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Table 2
Age periods when various lymphatic organs attain maximum size and regress

<table>
<thead>
<tr>
<th>Lymphatic organ</th>
<th>Maximum size</th>
<th>Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes</td>
<td>Adolescence</td>
<td>Slowly through adult life</td>
</tr>
<tr>
<td>Tonsils</td>
<td>Puberty</td>
<td>Primarily in 4th and 8th decades</td>
</tr>
<tr>
<td>Appendix</td>
<td>First decade</td>
<td>Slowly until the 7th decade</td>
</tr>
<tr>
<td>Spleen</td>
<td>Young adulthood</td>
<td>After the 7th decade</td>
</tr>
<tr>
<td>Thymus</td>
<td>Early childhood</td>
<td>Around puberty</td>
</tr>
</tbody>
</table>
results of the 2-time-period approach, it is unlikely to have a significant influence on the results of the index-secondary case approach.

An intriguing question that has not been considered is whether the stability (versus migration) of the population studied might be an important factor in the teacher-student study model. During the past 20 years, the characteristics of Nassau and Suffolk counties have changed in several ways. Thus, between 1950 and 1970, the population in this area has more than doubled, rural areas became rapidly urbanized and industrialized and, during the past decade, residents of these counties have generally been of high socioeconomic status. All of these changes can have profound effects on the patterns of certain infectious diseases. Furthermore, it should be recalled that outbreaks of certain viral diseases (i.e., influenza) can occur quite unexpectedly in certain communities following the arrival of apparently healthy travelers. That these observations are of potential relevance to Hodgkin's disease in the community is clear, since the level of urbanization is thought to influence the patterns observed for this disorder (6).

**Occupational Mortality Studies**

Preliminary evidence derived from occupational studies would also appear to be consistent with the possibility that Hodgkin's disease might have an infectious component. One of the hypotheses generated from the Nassau-Suffolk teacher-student study was that teachers might have an excessive risk for this disorder. Using proportionate mortality analysis, Milham (18) found that the number of teacher deaths due to this disorder among male residents of Washington State who were 20 years of age and older was significantly greater than that expected.

Medical personnel represent another occupational group that might be a high-risk group. One study in upstate New York found that mortality rates for physicians were significantly greater than rates for the general population, high socioeconomic counties, and dentists of the same age and sex (35). Another study in Great Britain did not find an excessive rate for physicians (28), and therefore additional study of this matter will be required.

Before leaving this subject, it is important to realize that, although the demonstration of higher rates for occupational groups in repeated contact with Hodgkin's disease patients can be interpreted as lending indirect support to the transmission hypothesis, the converse of this does not necessarily hold true. Thus, for example, in most sanitariums, physicians who have been in continual contact with patients with open tuberculosis have not developed this disease with excessive frequency (26). Furthermore, there does not appear to be any evidence that the incidence of clinical tuberculosis is significantly greater in medical students than in various other student groups (26), despite the fact that rather marked differences have been observed in different medical schools. These variations, as well as the frequent observation that tuberculosis rates have been excessively high for certain medical student classes but not others, indicate that even repeated exposure is insufficient in itself for the development of clinical tuberculosis. It seems clear that this is also true for Hodgkin's disease, since not one case of this disorder was observed among oncologists in upstate New York between the years 1960 and 1972 (35).

**Familial Studies of Hodgkin's Disease**

In an analysis of the 2 previous systematic surveys of familial Hodgkin's disease (7, 24), MacMahon (16) indicated that the 2 major patterns were sib-sib and parent-child, and that most patients were under 40 years of age at diagnosis. Comparison of the age and time intervals at diagnosis for sib pairs suggested that the latter was shorter, and this was interpreted as being more consistent with an environmental and possibly infectious interpretation, rather than genetic (with a specific age association). It was pointed out, however, that a major limitation in using the familial pairs derived from these hospital-based studies was the possibility that the cases identified might have been primarily those who were diagnosed close in time (16). To overcome this potential bias, the tumor registry of the Cancer Control Bureau, New York State Department of Health, was used to identify objectively all familial pairs with this disorder between 1950 and 1970 (31). Twenty-three familial pairs (46 cases) were identified, and the ages of patients ranged from 14 to 82 years, with 31 patients less than 40 years of age. There were 9 sib pairs, including 1 pair of identical twins, 7 parent-child pairs, and 4 instances in which patients were cousins. The 3 remaining familial pairs were nephew-uncle, nephew-aunt, and grandfather-granddaughter. While there was no prevalent pattern of concordance or discordance by sex, only 4 couples were both female. Analysis of the time and age differences (at diagnosis) for the 9 sib pairs indicated that the mean diagnostic interval was significantly shorter than the mean age interval. Another approach was to compare the median time intervals between diagnoses for the 4 parent-child and 3 sib pairs living in the same household prior to and at the time the 1st case was diagnosed (Group A) with that for the 6 sib and 3 parent-child cases who resided in the same county but not in the same household (Group B). The median time interval between diagnoses for Group A pairs was 1 year (mean, 1.2; range, 0.2 to 2 years) whereas, for Group B pairs, it was 3.4 years (mean, 4.1 years; range, 0.8 to 8.7 years). It would seem therefore that the results of all the systematic familial studies favor an environmental, and possibly infectious, interpretation. There are, however, 3 points that must be made about these and future studies of familial Hodgkin's disease. (a) The number of familial pairs identified to date is small and, therefore, caution is required in interpreting the results. (b) Detailed consideration should be given to all possible explanations for the apparent rarity of cases in husbands and wives. (c) A recent report (3) has identified a possible bias in comparing the time and age intervals for family pairs. Stated briefly, when the junior member of a familial pair is diagnosed first, the time interval between diagnoses will always be shorter than the age interval. While this fact does not alter the results of the analysis of time intervals between diagnoses by place of residence, it does make the need to develop new approaches in evaluating data derived from familial studies.
Discussion

A previous review indicated that the weight of epidemiological evidence is consistent with the possibility that Hodgkin’s disease is an infectious disorder (29). In this paper, the 4 epidemiological approaches used to evaluate this hypothesis and their limitations have been summarized, and some related questions have been raised. It is obvious, however, that these preliminary findings must be viewed in context with other observations. It seems clear that if an infectious agent does play an etiological role in Hodgkin’s disease, it is one of several essential factors. Available evidence suggests that genetic and racial factors, such as the presence of certain HL-A antigens of the 4C group (10) and Italian and Jewish ancestry (16) might be associated with an increased frequency of this disorder. Furthermore, certain congenital immune deficiency states, such as ataxia-telangiectasia and the Swiss-type of agammaglobulinemia, might be associated with an increased frequency of Hodgkin’s disease. A recent report (4) describes a large inbred family in which there were 7 cases of Hodgkin’s disease, 3 of lymphosarcoma, 2 of thymoma, 2 of common variable immunodeﬁciency, and single cases of 3 other cancers. How might these genetic factors be integrated with the concept of infectivity? An obvious possibility is that they might influence the susceptibility of certain individuals to oncogenic agents that initiate Hodgkin’s disease. An association of this type has already been demonstrated between the murine major histocompatibility complex H-2, and resistance to virus-induced leukemogenesis (17). It is also possible that genetic factors influence viral transmission. Hattis et al. (12) showed that there is a small number of individuals infected with rubella who have a high potential for spreading the virus, whereas most infected individuals have only minimal potential for spread. Honeymon and Menser (13) have postulated that the spreaders (with rubella) who infect most susceptibles with whom they come in contact are those possessing the HL-A1 and -8 haplotypes. Interestingly, places such as Hawaii, Malaysia, Taiwan, Jamaica, and Trinidad are characterized by both fewer epidemics of rubella than expected and low frequencies of HL-A1 and -8. As indicated above, Hodgkin’s disease is also characterized by ethnic variations in incidence and a high frequency of certain HL-A antigens, including the I and B haplotypes. Using linear regression analysis, the incidence of this lymphoreticular cancer in several ethnic groups was found to correlate significantly with the mean gene frequency of HL-A1 and -8. If Hodgkin’s disease does have an infectious component, with racial distribution of HL-A antigens controlling the degree of susceptibility and transmission, this could have a profound influence on the results of epidemiological, virological and immunological studies that attempt to determine the nature of this disorder. It seems clear that a variety of scientific disciplines will be required to answer these questions.

References

1. Abramson, J. H. Infective Agents in the Causation of Hodgkin’s Disease.


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