Current Epidemiological Evidence for Transmission of Hodgkin's Disease

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Summary

The epidemiological evidence relating to the possibility of person-to-person transmission of Hodgkin's disease is reviewed. A number of studies are found to be difficult to interpret because of the absence of control data. It is concluded that, although certain studies are consistent with the hypothesis of person-to-person transmission, the evidence is at present weak and further epidemiological studies are needed.

Introduction

The most important epidemiological question now regarding the nature of HD is whether the epidemiological data are indicative of, and consistent with person-to-person transmission of the disease.

The early studies of Razis et al. (13) suggested that the members of the immediate family of HD patients have about a 3-fold increased risk of developing the disease. Analysis of the data obtained by Razis (13) and later by MacMahon (9) on the times and ages of onset in pairs of siblings and of similar data obtained more recently by Vianna et al. (17) suggested an environmental rather than a genetic factor.

However, interest in the possibility of direct person-to-person transmission of HD was greatly stimulated by the observations of Vianna et al. (18, 19) in Albany. A situation described in which 31 HD patients, diagnosed in the period 1950 to 1970 could be “linked” together either through direct personal acquaintanceship with each other or through mutual friendship with an unaffected person. These 31 patients represented 15% of the 208 HD patients diagnosed in Albany County during this time.

This observation appeared remarkable and much more impressive than the many prior reports of “clusters” of leukemia. However, Vianna and his colleagues were the first to investigate HD in this way. They questioned patients with HD and their contacts, assuming that the disease might be infectious but with a possibly long latent period; whereas, for example, most of the previous searches for clusters of leukemia had depended on “related” cases having their onset of disease at a similar time. The approach was an important innovation, but the vital information that was lacking was how easy it would be to generate a similar set of linkages among a “random” selection of 208 residents of Albany County. The absence of these control data reduces the Albany cluster to essentially an anecdotal report, but nevertheless a very important one.

Since this original report, a number of other studies have been conducted along related lines but they have, unfortunately, tended to generate heat rather than light and the epidemiological picture still remains murky.

It is clearly important that the problems relating to such epidemiological studies be rapidly resolved, not only because of the scientific importance of the issue but also because of the public health implications. Much distress is being caused to HD patients and their relatives and friends by a belief that the disease is transmissible, when this is far from proven.

Anecdotal Observations: What is Their Significance?

Anecdotal reports may be of enormous value in the generation of hypotheses but, once this stage is past, such reports are usually of no value and may even be counterproductive of a proper test of the generated hypothesis. The literature abounds with anecdotal reports of clusters of cases of leukemia but, when well-defined, unselected populations have been studied, tests of space-time clustering have either been negative or so weakly positive as to be possibly all explained away as artifacts (3). Among the most well-known leukemia clusters are those in Niles, Ill. (4), and Orange, Texas (5), but Glass et al. (3), in a study of cases of childhood leukemia in Los Angeles, demonstrated that, although overall their data showed no evidence of clustering, by selecting suitable adjacent census tracts and by paying attention to the number of cases in each tract, 9 areas could be retrospectively defined in which the incidence of the disease was as high as in Niles or Orange County. The implication is that such clusters may well represent no more than chance aggregations of cases and probably exist all over the U. S.

Similarly, the reports that groups of HD patients have had prior contact with each other are impossible to interpret because we do not know how easy it is to link people without HD in this way. We have shown previously (16) that if we assume that, on the average, a new HD patient has had “contact” with 500 people in the preceding 10 years then, by chance alone, about 20% of all HD patients might be
expected to have had contact with another person who develops HD in that period. Of course, the assumption of 500 contacts is arbitrary because there are no good data on which to base such an estimate. If we extend the search for linkages outside of HD patients alone and include all leukemia and lymphoma patients, as was done in a study recently reported by Schimpff et al. (14) relating to such patients in 3 areas of rural Virginia, then even more conservative assumptions yield perhaps surprising results.

Assume that each new patient has 100 close contacts or acquaintances (and in this category have been included siblings, parents, children, grandparents, grandchildren, nephews, uncles, great uncles, etc., neighbors, wives, girlfriends, boyfriends, roommates, lodgers, babysitters, workmates, and other friends, so that 100 does not seem an unreasonably high number); in a 10-year period we would expect about 0.2 case of leukemia/lymphoma among the close contacts of each patient (assuming an incidence rate of 20/100,000/year, Connecticut Cancer Registry (2)). That is, 20% of patients will have had close acquaintance with a person developing the disease in a 10-year period, or 40% in a 20-year period. If we go 1 step further and assume that each of a patient's close contacts themselves each have 100 close contacts, we would expect, by chance alone, about 20 cases of leukemia/lymphoma among the 10,000 indirect contacts associated with each patient. Of course, this computation carries many assumptions, in particular that each contact has 100 different contacts; but even if we reduce the expected number of associated cases by 20-fold, we still expect to have 1 indirect link associated with each patient.

The only point of the above calculations is to illustrate that the apparent impressiveness of the linkages described in studies such as those of Vianna et al. (18, 19), Parker (11), and Schimpff et al. (14) may be illusory.

What is Statistically Significant?

Another difficulty of interpretation arises when statistical significance levels are associated with essentially anecdotal reports. If 20 people look among a small series of cases for an unusual situation (defined as \( p < 0.05 \)) then, on the average, 1 will find it and publish it and the other 19 will not. Klinger and Minton (7) reported statistically significant clustering (\( p < 0.02 \)) of 5 cases of HD among a series of 12 patients in Union County, Ohio. It is very doubtful whether the authors would have submitted the paper, or the journal would have published it, had it been a "negative" finding among 12 cases. We do not know how many other people were looking for a similar situation, but a rough calculation suggests that, if we divide the United States into areas with the same population as Union County, then in about 160 of these areas a situation at least as extreme as that in Union County would have been observed by chance alone (16).

Nonanecdotal Observations

Following the description of the "outbreak" of HD centered around Albany High School, Vianna and Polan (20) examined the distribution of people with HD according to the school they attended in Nassau and Suffolk counties of New York State. Their findings appeared to offer considerable support to their earlier observations. Eight secondary schools had HD patients in attendance in the period 1960 to 1964. Five of these schools had further cases among students in the period 1965 to 1969. Sixteen matched control schools, selected because they had no cases in the earlier time period, had no cases occurring among students in the 2nd time period. This difference was statistically significant. Also, by adopting an alternative method of analysis, Vianna and Polan were able to show that the subsequent incidence of HD among persons attending a school at the same time as a diagnosed patient was 2 to 3 times the expected rate. This study has been criticized on the basis of a possible underascertainment of cases (12) which could lead to bias if the loss of cases were nonrandom. However, Vianna and Polan (21) feel that this is not a major bias, and it is true that some of the other biases inherent in a study of this kind (particularly those relating to migration) will tend to act against a positive finding. The importance of this study is 2-fold. First, it offers some support for the earlier anecdotal data and, second, the design of the study was such that it may be replicated and such studies may be statistically evaluated. It is in fact the only published study at this time that directly relates to the earlier observations and for which a reasonable attempt at a statistical evaluation may be made. Very similar studies are now under way in Boston and England, and it is likely that these will clarify the issues relating to the risks of HD and school attendance.

Other studies relating indirectly to the possible person-to-person transmission of HD have, at best, been weakly positive. No evidence of space-time clustering has been found in 2 large studies (1, 8), but this is to be expected if the latent period of the disease is possibly long and variable. Vianna et al. (22) have argued that doctors necessarily have an increased exposure to patients with HD after their diagnosis and these authors have demonstrated a raised death rate from HD among physicians in New York State in the period 1960 to 1972. However, a prospective study of 34,445 British doctors over a 15-year period has shown no excess deaths from HD and smaller studies of radiotherapists in both the United States and Britain have shown no excess risk among these groups who might be expected to have above-average occupational contact with HD patients (15).

Milham (10), in a study of proportionate mortality, reported a 2- to 3-fold increase in risk of dying of HD among school teachers in Washington State and interpreted this observation as supporting the "infectious" hypothesis, presumably on the assumption that school teachers have above-average contact with young people and, therefore, above-average contact with young people with HD. However, reanalysis of the data by Hoover (6) suggested that much of the excess could be explained by Milham's use of proportionate mortality analysis, because teachers have a mortality from all causes of death combined that is considerably lower than that of the general population. An analysis based on census data indicated a much-reduced excess death rate from HD among teachers.
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Discussion

If we assume that the anecdotal observations are not chance effects and suggest person-to-person transmission of HD (and it must be emphasized that, in our opinion, the epidemiological evidence at the present time does not offer great support for this assumption), then it is possible to speculate about the existence and nature of any transmissible agent that might be involved (16). The study of Vianna and Polan (20) is the only study at present offering direct support to the anecdotal observations suggesting person-to-person transmission of HD, but it is important to stress that even if clustering of cases in schools is a real phenomenon there are hypotheses other than person-to-person transmission of the disease that must be given at least equal weight.

The outstanding need is for further epidemiological studies to either confirm or refute the findings of the Albany group. If their findings do not represent chance observations, it will be important to identify the periods of infectivity and the latent period associated with the disease. In particular it will be important to know, both for possible laboratory studies and for reasons of public health, if patients are infective after diagnosis of the disease.

References

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